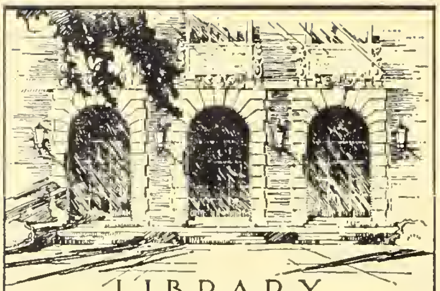

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ORGANIC SEMINAR ABSTRACTS

1966-67

Semester II

Department of Chemistry and Chemical Engineering

University of Illinois

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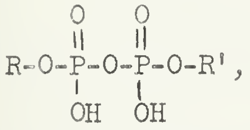
MECHANISMS IN THE BIOLOGICAL CHEMISTRY OF PYROPHOSPHATE ESTERS

Reported by W. T. Shier February 23, 1967

Introduction:

For decades physical organic chemists have studied the mechanisms of the reactions they conducted in their flasks, often determining to a high degree of certainty the detailed path of the atoms and electrons involved in these conversions. In contrast the mechanisms of the reactions of many biologically important functional groups have been largely ignored even to the present day. One such group is the pyrophosphate group.

The pyrophosphate esters found in nature may be represented by the formula



$$R{-}O{-}\overset{\overset{O}{\|}}{\underset{\underset{OH}{|}}{P}}{-}O{-}\overset{\overset{O}{\|}}{\underset{\underset{OH}{|}}{P}}{-}O{-}R',$$

where, depending on the stratagems of nature, R or R' may be as simple as a proton or as complex as a nucleoside. The pivotal role of phosphorus compounds in the chemistry of life was first recognised by Fritz Lipmann, and represents, perhaps, one of his greatest contributions to the understanding of the chemistry of biological systems. As will be shown, pyrophosphate esters and the pyrophosphate ion itself are endowed with unique biochemical properties.

These compounds have heretofore invariably been considered in various other contexts, usually based on some non-functional portion of the molecule. When considered as pyrophosphate esters, they represent a large and disjointed group of natural products. A method of organizing and correlating this heterogeneous array is offered by a rapidly emerging branch of Organic Chemistry, Bioorganic Mechanisms - that hybrid of Physical Organic Chemistry and Enzymology[1]. On the basis of mechanistic aspects of the biological function of these compounds they have been correlated into three groups and their biological reactions organized by three general equations.

The Role of the Pyrophosphate Ion as a Leaving Group:

The pyrophosphate ion functions as a leaving group in many biosynthetic coupling reactions. Typical is the biosynthesis of nucleoside coenzymes[2], which can be represented schematically as:

$$\text{nucleoside-O-P-P-P} + \text{R-O-P} \rightleftharpoons \text{nucleoside-O-P-P-OR} + PP_i$$

The role of the pyrophosphate ion as a leaving group in a similar substitution reaction has been studied by Lipmann.[3] In the biosynthesis of adenosine-5'-phosphosulfate (APS) in a yeast extract preparation, the thermodynamics of the

---

Abbreviations and structural symbols used in this work:
-OPP, pyrophosphate monoester; P_i, inorganic phosphate; $OPP^{\ominus}$, inorganic pyrophosphate; Enz-SH, sulfhydryl-containing enzyme; NAD, nicotinamide adenine dinucleotide; NADP, (TPN) nicotinamide adenine dinucleotide phosphate; PRPP, 5-phospho-ribosyl-1-pyrophosphate; -OP, phosphate monoester; CDP, cytidine diphosphate; CMP, cytidine monophosphate; UDP, uridine diphosphate; CoA, coenzyme A; TPP, thiamine pyrophosphate; FAD, flavin adenine dinucleotide; ATP, adenosine triphosphate; ADP, adenosine diphosphate; AMP, adenosine monophosphate; DCC, dicyclohexylcarbodiimide.

equilibrium

$$\mathrm{ATP} + \mathrm{SO_4}^{=} \overset{\text{ATP-sulfurylase}}{\rightleftarrows} \mathrm{APS} + \mathrm{PP_i}$$

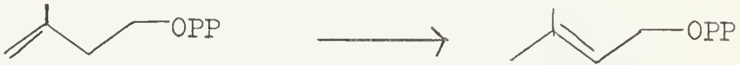
strongly favor the reverse reaction. When pyrophosphatase was added to a purified ATP-sulfurylase system, the equilibrium concentration of APS increased from 0.01μM./ml. to 0.23μM./ml.[3] Thus, the pyrophosphatases, which catalyse the very exothermic hydrolysis of the pyrophosphate ion, provide an energy coupled system with a sufficient over-all free energy drop to favor APS synthesis.

Pyrophosphate Esters as Coupling Intermediates:

Polyisoprenoids can be considered to be biosynthesized by means of the polymerization in defined modes of Δ^3isopentenyl pyrophosphate monomer.[4] The intermediacy of these pyrophosphate esters in the biosynthesis of squalene has been demonstrated by Lynen and his collaborators.[5,6] When 2-^{14}C-mevalonate-5-phosphate was added to a crude enzyme system from yeast, labeled farnesyl pyrophosphate and geranyl pyrophosphate were isolated by paper chromatography and identified by comparison with synthetic standards.[5] When the system was inhibited with iodoacetamide Δ^3isopentenyl pyrophosphate accumulated.[6] A sulfhydryl-containing enzyme was isolated in crude form which converted Δ^3isopentenyl pyrophosphate into dimethylallyl pyrophosphate. The proven and postulated products of Δ^3-isopentenyl pyrophosphate polymerization are summarized in the following table:[7]

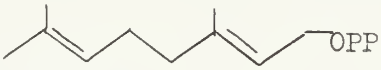
Degree of Polymerization:

n=1



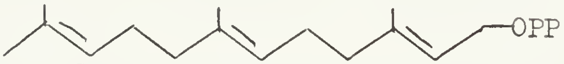
Δ^3-isopentenyl pyrophosphate

n=2



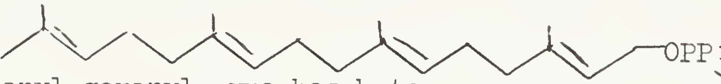
Geranyl pyrophosphate → Monoterpenoids

n=3



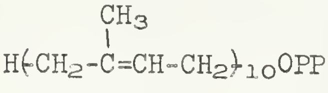
Farnesyl pyrophosphate → Sesquiterpenoids
→ Squalene

n=4



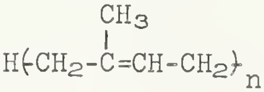
Geranyl-geranyl pyrophosphate → Diterpenoids
→ Complex Lipids[15]
→ Phytoene

n=10



$\mathrm{H(CH_2\text{-}\overset{\displaystyle CH_3}{\overset{|}{C}}{=}CH\text{-}CH_2)_{10}OPP}$ → Ubiquinones

n=n



$\mathrm{H(CH_2\text{-}\overset{\displaystyle CH_3}{\overset{|}{C}}{=}CH\text{-}CH_2)_n}$ → Gutta percha

The driving force for the condensation of monomer units has been attributed to the unique effectiveness of the pyrophosphate ion as a leaving group.[8] It is contended here that this ability may result not so much from any chemical property of the pyrophosphate ion, as from its rapid removal from the system by highly active, widely distributed pyrophosphatases. The pyrophosphate concentration can reasonably have a profound effect on the pyrophosphate ion-eliminating mechanism in the enzyme-substrate complex, thus inhibiting the overall reaction. Again, the pyrophosphatases may energy couple the hydrolysis of the pyrophosphate ion to carbon-carbon bond formation.

These condensation reactions can be summarized by general equation I:

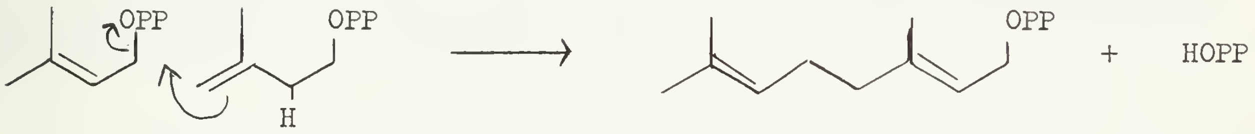
$$R\text{-}OPP + H\text{-}S: \rightleftharpoons R\text{-}S: + HOPP$$

$$\downarrow \text{Pyrophosphatase}$$

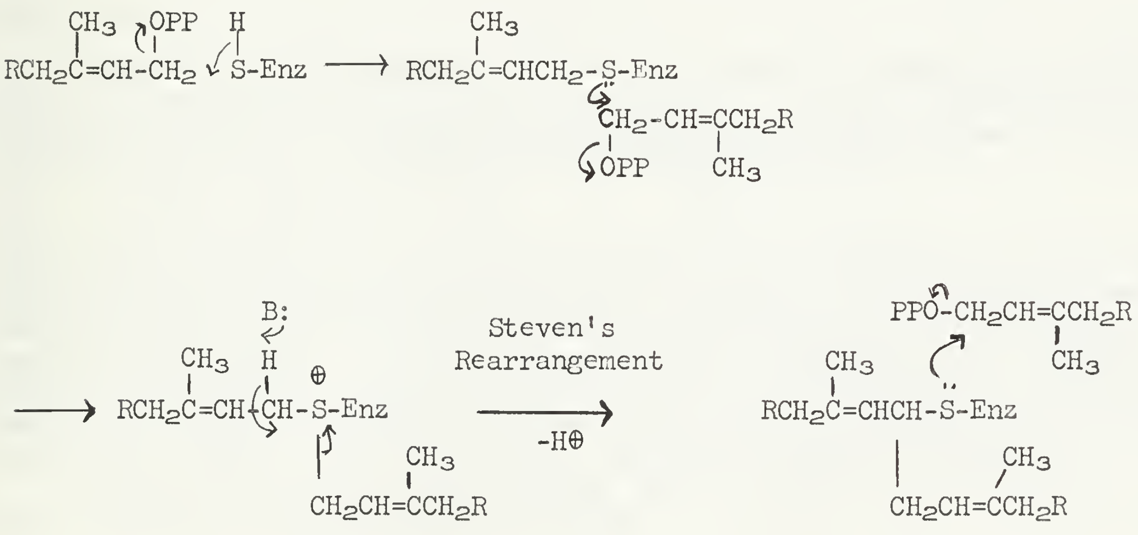
$$2P_i$$

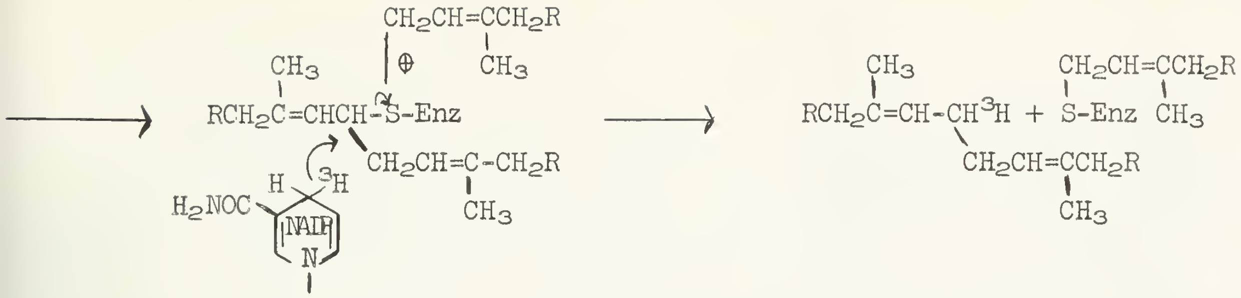
In this equation it is tempting to consider H-S: a general nucleophile. Since Yuan and Block observed a 63% conversion of $1\text{-}^3H\text{-}\Delta^3$-isopentenyl pyrophosphate to squalene in a yeast autolysate,[9] the rate of the biological reaction is greater than the rate of non-enzymatically assisted dissociation, which would result in hydrolysis to isopentenol. Hence, a strict S_N1 mechanism is ruled out, although an anchimerically assisted dissociation of the pyrophosphate ester as the enzyme-substrate complex is not. The absence of any isomeric reaction product[4] arising from allylic rearrangement in squalene biosynthesis also argues against any S_N1 mechanism, although Ingraham has suggested that the cationic species may be bound to the surface of the enzyme in a manner that permits further attack only at the terminal carbon.[10] It has been also suggested[8] that a cationic species is formed, but that its formation is concerted with the formation of a carbon-carbon bond; that this is anything other than an S_N2 mechanism is not made clear.

General equation I can be seen to describe the polymerization of Δ^3-isopentenyl pyrophosphate by considering head-to-tail condensation as resulting from nucleophilic attack by the π electrons of the double bond of the monomer either directly on the esterified carbon of the growing chain[12], or on an enzyme-growing-chain complex:


OPP
OPP
H
OPP
+
HOPP

The head-to-head reductive condensation of farnesyl pyrophosphate to produce squalene according to Cornforth's hypothetical scheme[13] can be seen to follow general equation I:


CH3
OPP
H
RCH2C=CH-CH2
S-Enz
RCH2C=CHCH2-S-Enz
CH2-CH=CCH2R
OPP
CH3
B:
CH3
H
⊕
RCH2C=CH-CH-S-Enz
CH3
CH2CH=CCH2R
Steven's
Rearrangement
-H⊕
PPO-CH2CH=CCH2R
CH3
CH3
RCH2C=CHCH-S-Enz
CH3
CH2CH=CCH2R



(R=Geranyl; B=proton acceptor, possibly part of the active site)

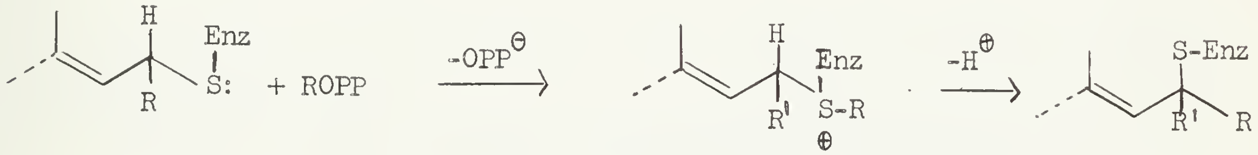
This mechanism satisfies a considerable body of compelling but not conclusive evidence obtained largely by Popják and collaborators.[14] The observations and conclusions are:

(1) The biosynthesis of squalene from farnesyl pyrophosphate by washed rat liver microsomes was powerfully inhibited by p-chloromercuri-benzoate, N-ethylmaleimide and Cu^{++} ions but not by iodoacetamide. Hence, the active site of the enzyme contains a functional S-atom, but not a free-SH, which would permit inhibition by iodoacetamide.[14]

(2) When squalene was biosynthesized in the same system from 5-^2H_2-mevalonate, 11 atoms of ^2H, not the theoretically possible 12, were retained. Mass spectroscopic analysis of succinate derivatives obtained from the centre of the chain by ozonolysis of the deuterosqualene showed mostly trideutero molecules. Hence, the labeling at the centre is $-CHD-CD_2-$.[14]

(3) In the biosynthesis of squalene from farnesyl pyrophosphate no tritium from H^3HO was incorporated into squalene, while incorporation of up to 0.8 μg-atom of the tritium per μg-mole of squalene from labeled TPN^3H was observed.[14] Hence, the condensation is a reductive process involving TPNH.

In Cornforth's mechanism, in the steady state all the experimental observations are satisfied. It may further be noted that in each -OPP eliminating step general equation I is followed. That is



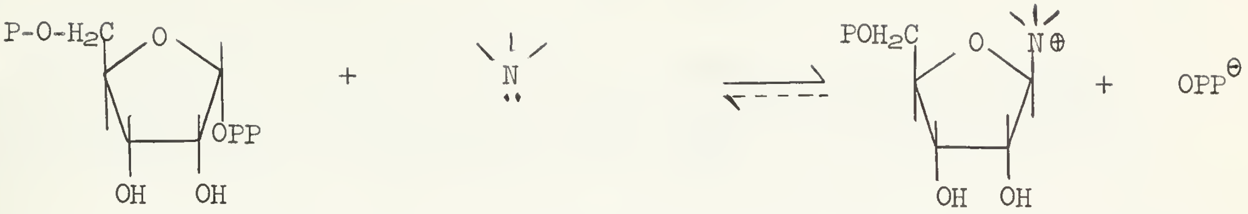
Where R=farnesyl and R' = H or farnesyl.

Reactions of pyrophosphate esters other than the synthesis of carbon-carbon bonds can be shown to follow general equation I. In the biosynthesis of a complex phospholipid from *Halobacterium cutirubrum* an ether linkage is formed by phytanyl pyrophosphate and an -OH of glycerol-1-phosphate.[15]

i.e. $R\text{-}OPP + H\text{-}\ddot{O}\text{-}C\!\lt \longrightarrow R\text{-}O\text{-}C\!\lt \quad + \quad HOPP$

Since the biosynthetic studies were carried out in a crude cell-free extract with the above reaction monitored only by analysis of ^{32}P incorporation into the final product, no detailed mechanism for the formation of the ether linkage has been put forward. It was observed, however, that the use of phytanyl pyrophosphate removed the requirement for ATP in the biosynthesis. Hence, the esterified pyrophosphate group supplies the energy for condensation. It can readily be seen, also, that the reaction conforms to general equation I.

In the biosynthesis of nucleotides, PRPP condenses with glutamine, orotic acid, purines, or pyrimidines as follows:



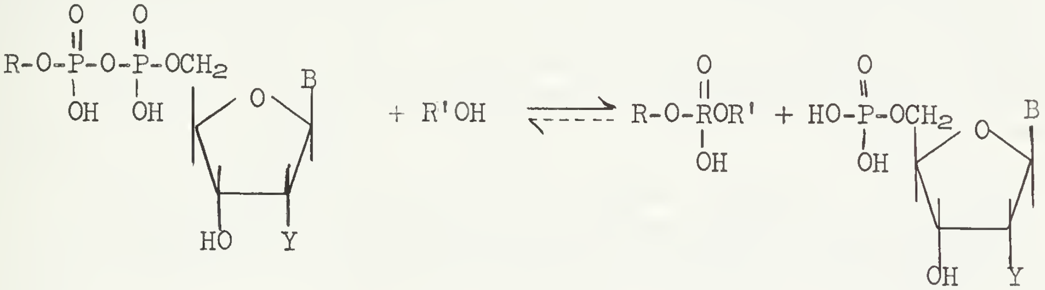
The problem of strict application of the terms of physical organic chemistry arises. Despite the fact that the leaving group is α to a heteroatom[16] a strict S_N1 reaction is highly unlikely. According to the Michaelis-Menten hypothesis,[17] in the biological reaction only PRPP is bound to the enzyme; the N-containing species also binds to the enzyme surface where reaction occurs. An S_N2 displacement of $OPP^\ominus$ by the lone pair of the N-containing species, while it and PRPP are both bound to the enzyme is the simplest mechanism, although not the only one possible.

It is observed that inversion of configuration occurs establishing the stereochemistry observed in nucleotides.[18] This inversion of configuration is consistent with an S_N2 mechanism, but not conclusive evidence for it.[11]

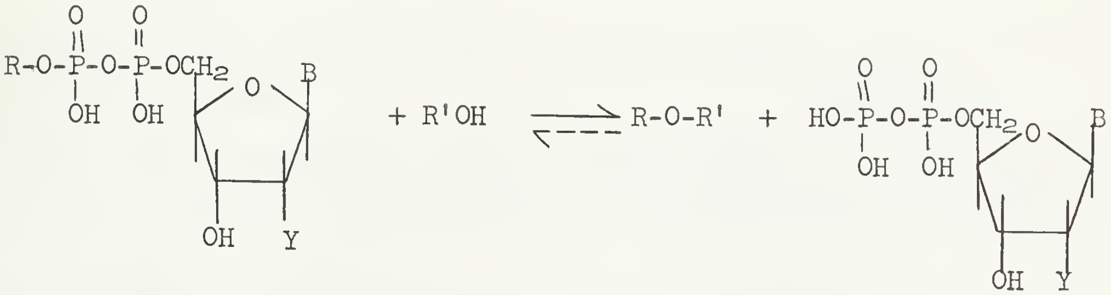
Group Transfer Intermediates:

The nucleoside pyrophosphate diesters represent a large and rapidly increasing group of biosynthetic intermediates. While the basic forms - the nucleoside diphosphate -sugars, -alcohols and -diglycerides - were known a decade ago, and extensively reviewed then,[19] studies demonstrating their universal involvement in the biosynthesis of complex lipids, oligosaccharides, homo- and hetero-polysaccharides in all levels of life, from the cell walls of *Neurospora crassa*[20] to the complex lipids of the human brain,[21] have occupied the time of hundreds of research workers in the intervening years. To introduce order into this thriving jungle of biosynthetic pathways, the following general equations are presented:

II



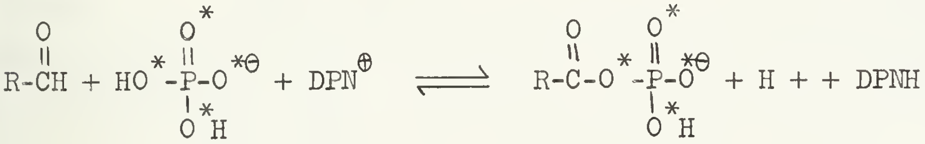
III



Y= -H or -OH; B= purine or pyrimidine

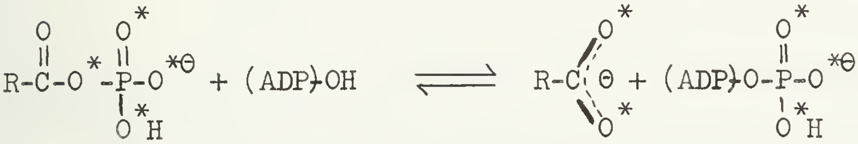
Neither of these type reactions has received direct mechanistic study. Results obtained for analogous systems will be considered, and the results obtained tentatively applied to the two general equations pending the appearance of systematic studies of these systems.

The alcoholysis of anhydride phosphate linkages has not been studied in biological systems,[22] but Cohn showed that ^{18}O labeled phosphate underwent isotope exchange with the carboxylate oxygen atoms of 3-phospho-glycerate in the following oxidative phosphorylation of ADP.[23]



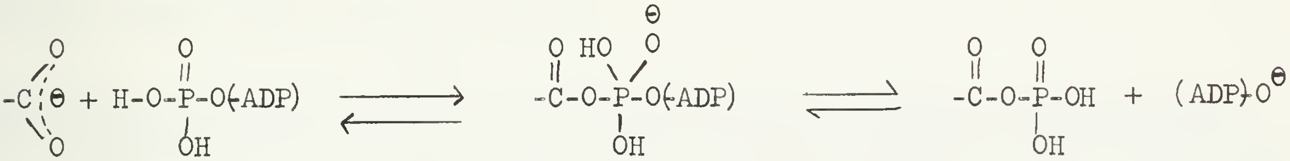
$$R\text{-}\overset{\overset{O}{\|}}{C}H + HO^{*}\text{-}\underset{O^{*}H}{\overset{\overset{O^{*}}{\|}}{P}}\text{-}O^{*\ominus} + DPN^{\oplus} \rightleftharpoons R\text{-}\overset{\overset{O}{\|}}{C}\text{-}O^{*}\text{-}\underset{O^{*}H}{\overset{\overset{O^{*}}{\|}}{P}}\text{-}O^{*\ominus} + H^{+} + DPNH$$

$R = -CH(OH)CH_2OPO_3H_2$



$$R\text{-}\overset{\overset{O}{\|}}{C}\text{-}O^{*}\text{-}\underset{O^{*}H}{\overset{\overset{O^{*}}{\|}}{P}}\text{-}O^{*\ominus} + (ADP)\text{-}OH \rightleftharpoons R\text{-}C(O^{*})_2^{\ominus} + (ADP)\text{-}O\text{-}\underset{O^{*}H}{\overset{\overset{O^{*}}{\|}}{P}}\text{-}O^{*\ominus}$$

The reverse of the second reaction was interpreted as nucleophilic attack by the carboxylate oxygens on the terminal P atom of ATP.[22] That is,



Extending this finding to the alcoholysis of anhydride phosphate linkages, nucleophilic attack by the oxygen of the alcohol on the appropriate phosphorus atom can be put forward as a working hypothesis for further research. One experiment which suggests itself consists of feeding $R^{18}OH$ to an active cell free extract containing the appropriate nucleoside diphosphate ester; identification of ^{18}O in excess in the phosphate diester and not in the nucleoside monophosphate would support the hypothesis.

In a transfer reaction analogous to general equation III Douderoff, Barker and Hassid explained the isotope exchange between $KH_2{}^{32}PO_4$ and glucose-1-phosphate in a sucrose phosphorylase preparation from Pseudomonas saccharophila in the absence of fructose, the phosphate acceptor, in terms of a glucosyl-enzyme complex.[24]

i.e. Glucose-1-$OPO_3\overset{-}{H}$ + Enzyme $\rightleftharpoons$ Glucose-Enzyme + $H_2PO_4^-$

(Glucose-1-$O^{32}PO_3\overset{-}{H}$) $\qquad$ ($H_2{}^{32}PO_4^-$)

The analogous substrate-enzyme complex has been suggested for systems described by general equation III.[25] The irreversibility of the reaction prevents the use of ^{32}P-labeled nucleoside pyrophosphate in an experiment analogous to that of Douderoff et al.[24]

The interesting question of whether P-O or C-O cleavage occurs could be answered by preparing the appropriate nucleoside triphosphate labeled with ^{18}O in the phosphate(s), adding it to a cell-free extract, and analysing R-O-R' for excess ^{18}O; excess ^{18}O would indicate P-O cleavage.

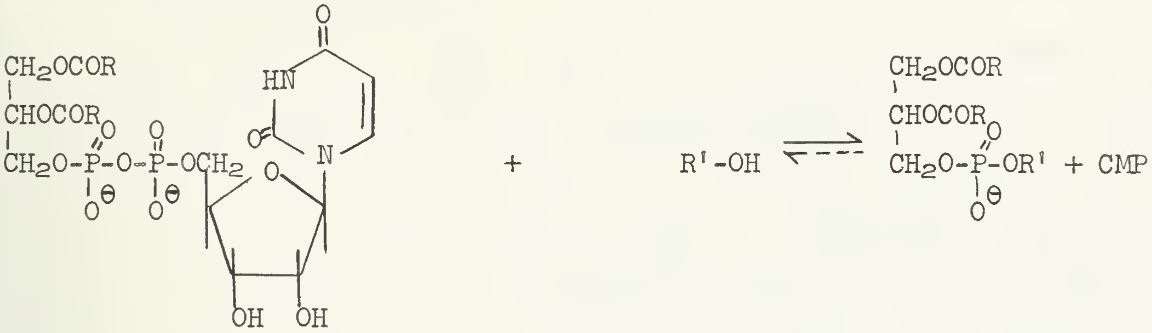
The nucleoside pyrophosphates function as transfer intermediates in some reactions.

For example, the following kinase catalysed reaction[2] fits general equation II:

2 nucleoside-OPP $\rightleftharpoons$ nucleoside-OP + nucleoside-OPPP

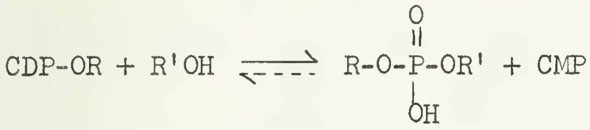
This reaction is general to both nucleoside and deoxynucleoside pyrophosphates.[2]

Phosphatides are biosynthesized from CDP-diglycerides[26] according to the scheme of general equation II:



where R = $CH_3(CH_2)_{14}$, for example, and R'OH = L-α glycerol, L-serine, myo-inositol or phosphatidyl glycerol.[26]

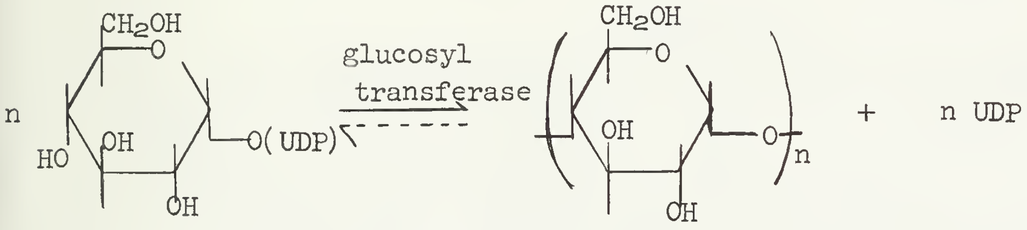
Other cytidine diphosphate alcohols also undergo enzymatic conversions[26] according to the scheme of general equation II:



$$\mathrm{CDP\text{-}OR} + \mathrm{R'OH} \rightleftharpoons \mathrm{R\text{-}O\text{-}\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle OH}{|}}{P}}\text{-}OR'} + \mathrm{CMP}$$

where ROH is ethanolamine or choline in an alternate synthesis of lecithins,[26] or α-glycerol or 5-ribitol in the biosynthesis of bacterial cell wall polymers.[27]

The nucleoside diphosphate-pentoses and -hexoses represent the largest group of transfer intermediates[19] - they are found for most of the known nucleosides and deoxynucleosides.[19] The sugar moieties include hexoses, pentoses, glycuronic acids, hexosamines, mucopeptides and oligosaccharides[28] attached to the pyrophosphate moiety at the anomeric carbon. They undergo reaction according to the scheme of general equation III. For example, the synthesis of glycogen from UDP-glucose in rat liver:[29]

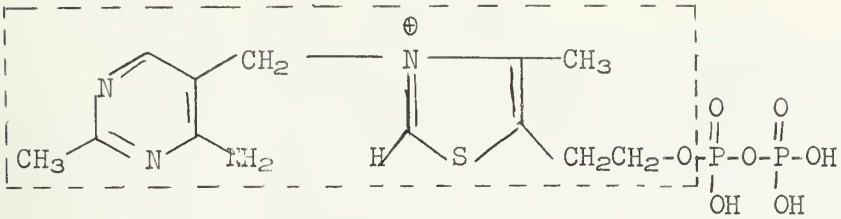


"Non-Functional" Pyrophosphate Esters:

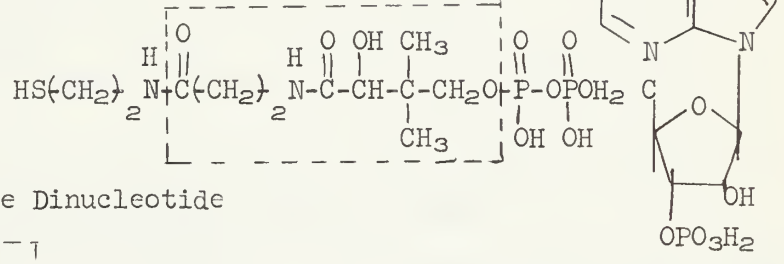
This group of pyrophosphate esters consists largely of the coenzymic form(s) of the B vitamins.[30] The term "non-functional" is somewhat of a misnomer, for the pyrophosphate moiety serves as a linkage in some cases (e.g. CoA, NAD, FAD, etc.), it may serve as a binding site to attach the coenzyme to the enzyme (e.g. TPP), or it may become functional after conversions have been made on other parts of the molecule (e.g. mevalonate-5-PP).[12] On any account, however, the pyrophosphate group does not undergo a permanent change in the normal biological function of the molecule.

In the conversion of the B vitamins to their coenzymic forms the vitamin is usually incorporated intact:[30]

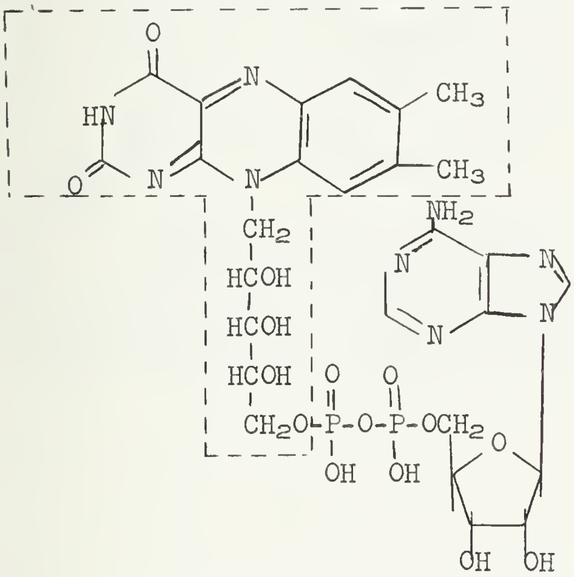
Vitamin B₁ → Thiamine Pyrophosphate



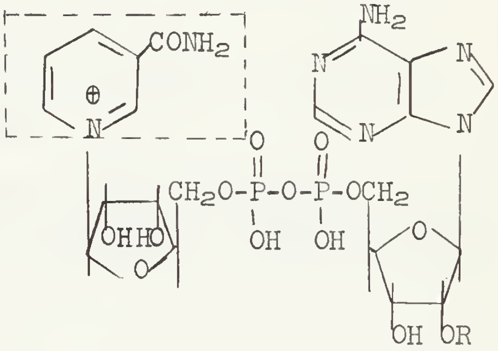
Pantothenic Acid → Coenzyme A



Riboflavin → Flavin Adenine Dinucleotide



Niacin → Nicotinamide Adenine Dinucleotide



R = H : NAD

R = $-PO_3H_2$: NADP

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THE CONFIGURATIONAL STABILITY OF ALKENYL RADICALS

Reported by Peter M. Harvey February 27, 1967

INTRODUCTION

There is evidence in the literature that aliphatic radicals generated at optically active carbon atoms are unable to maintain their initial configurations, and that they yield racemic products.[1] In view of the known configurational stabilities of alkenyllithiums[2] relative to alkyllithiums,[3] it is of interest to examine whether alkenyl radicals are configurationally more stable than alkyl radicals. This seminar will review the evidence for the nonlinearity of vinyl and substituted vinyl radicals and will discuss chemical studies in which isomeric alkenyl radicals are generated and captured.

If it can be established that the vinyl radical is nonlinear and does not maintain its configuration, the question of whether loss of configuration occurs by rotation or by inversion is not a trivial one. Although no experiments have been reported which distinguish between the two pathways, one might expect the isomerization to proceed by inversion, with a simple migration of the α-substituent to an alternate site of high electron density, rather than by rotation, in which the π-bond of the vinyl group must be broken. The question of inversion vs. rotation will not be dealt with further in this review, and for convenience the term "inversion" will be used to refer to the interconversion of isomeric alkenyl radicals, regardless of the mechanism.

ELECTRON SPIN RESONANCE STUDIES

The ESR spectrum of the vinyl radical should show eight lines if the three hydrogen atoms are nonequivalent or six lines if the two β-hydrogen atoms are equivalent. Fessenden and Schuler irradiated liquid ethylene with 2.8 Mev electrons in the cryostatted cavity of an ESR spectrometer.[4] Near 104°K they observed superimposed on the twelve-line spectrum of the ethyl radical a doublet of doublets which they attribute to the vinyl radical; the apparent hyperfine splittings of 102.44 and 13.39 gauss were not significantly temperature dependent. The formation of butane, 1-butene, and 1-hexene during the electron irradiation of ethylene at 105-163°K has been cited as evidence that ethyl and vinyl radicals are indeed formed.[5] Furthermore, vinyl radicals have been trapped with labelled methyl radicals generated from iodomethane-C^{14} during the electron irradiation of liquid ethylene.[6]

The center of the nine-line pattern attributed to the trideuteriovinyl radical from the irradiation of ethylene-d_4 was displaced 0.40 gauss from that of the unlabelled species. Fessenden and Schuler attribute this shift upon isotopic substitution to a second-order effect which can be rationalized if the 102.44 gauss splitting represents the sum of two approximately equal coupling constants. If the α-proton of the vinyl radical is inverting with a frequency comparable to the difference of two nonequivalent β-proton splittings, then the inversion effectively interchanges the two β-protons and causes a change in the spin state when the two β-protons are antiparallel. As a result, the inner four lines corresponding to these spin states are broadened, leaving a spectrum whose major splitting corresponds to the sum of the two β-proton splittings. If this interpretation is correct, the 13.39 gauss splitting can be assigned to the α-proton.

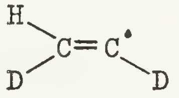
The vinyl radical spectrum was also observed when liquid ethane containing 0.5% acetylene was irradiated. No signal attributable to the 1,2-dideuteriovinyl radical was observed in a similar experiment employing acetylene-d_2; this result is consistent with an inverting radical in which all the lines are broadened beyond detection. Hence Fessenden and Schuler conclude that the vinyl radical is nonlinear and that the α-proton is rapidly inverting. They feel that the hybridization on the α-carbon atom is intermediate between sp^2 and sp and probably lies close to the former. By estimating the combined line widths of the broadened lines to be on the order of fifty gauss, they place limits of $3x10^{-8}$ and $3x10^{-10}$ sec on the lifetimes of the individual configurations. Assuming a classical model and a normal preexponential factor of about 10^{13} sec^{-1} (i.e., $\Delta S^{\ddagger} \approx 0$), this range of lifetimes corresponds to a barrier to inversion of about 2 kcal/mole; if the lifetime of a single configuration

is limited by quantum-mechanical tunnelling,[7] this figure represents a lower limit on the estimated barrier height.

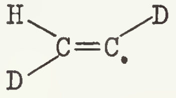
The electron-beam irradiation of a 2.5-mole-% solution of allene in liquid ethane at 101°K gave rise to an ESR signal which was interpreted as a superposition of the spectra of the ethyl, 2-propenyl (α-methylvinyl), 3-propynyl, and allyl radicals.[4] The sixteen lines attributed to the 2-propenyl radical can be grouped into four equally intense, overlapping 1:2:2:1 quartets; this pattern is consistent with a slowly (on the ESR time scale) or noninverting nonlinear radical. The lowering of the inversion rate when a methyl group is substituted for the α-proton of the vinyl radical is consistent with a tunnelling mechanism for inversion. The hyperfine splittings for the 2-propenyl radical are 19.48, 32.92, and 57.89 gauss; the latter two values are assigned to the two β-protons since their sum is similar to the sum of the two β-proton hyperfine splittings in the vinyl radical.

Cochran, Adrian, and Bowers generated the vinyl radical at 4.2°K by ultraviolet irradiation (2537 A°) of a solid argon matrix containing 1% hydrogen iodide and 9% acetylene.[8] They observed a complex unsymmetrical spectrum but were able to assign the eight-line gross pattern to three nonequivalent protons. Other workers observed a similar spectrum in the solid phase at 77°K after atomic hydrogen generated in a silent electrical discharge had been allowed to react with acetylene at 20°C in the gas phase or at -196°C in the solid phase.[9] The complexity of the spectrum presumably arises from the failure of anisotropic dipolar interactions to average to zero through rapid thermal tumbling. The hyperfine splittings due to the three protons are 15.7, 34.2, and 68.5 gauss;[10] these values are in good agreement with the values given above for the α-proton and the sum of the β-proton hyperfine splittings for the vinyl radical in the liquid phase. In the solid phase at 4.2°K the inversion is apparently slowed or frozen so that two distinct β-proton couplings are observed.

When a mixture of hydrogen iodide and acetylene-d_2 was photolyzed under similar conditions, the ESR spectrum consisted of two groups of lines separated by approximately 64 gauss. The spectrum became weaker as the temperature was raised to 32°K, but no new lines appeared. Addition of a hydrogen atom to the acetylene molecule can give rise to either or both isomeric vinyl radicals *I* and *II*. The absence of any lines with splittings of 34 or 16 gauss was rationalized[8] to require that *only one* species, the isomer (*I* or *II*) whose β-proton gives rise to the 64 gauss splitting, is present in detectable amounts. If inversion of the vinyl radical is a tunnelling phenomenon,[7] the rate of inversion should be relatively temperature independent, since there is no classical activation energy requirement. An inversion process that is rapid near 100°K in the liquid phase but slow enough to maintain configuration at 4.2°K in the solid phase is not consistent with a tunnelling mechanism unless the transition from liquid to solid at 4.2°K is accompanied by an additional stabilization of the predominant radical relative to the transition state for inversion of at least 150 cal/mole.



I

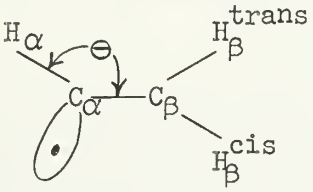


II

A single predominant isomer might be the kinetically-determined product of specific *cis* or *trans* addition of the hydrogen atom, or it might be the thermodynamically more stable radical. Cochran, Adrian, and Bowers feel that neither of these explanations is entirely satisfactory. They believe that the addition of a hydrogen atom to a molecule of acetylene is exothermic and should give rise to a vibrationally excited vinyl radical, which should invert rapidly before being cooled to 4.2°K; they do not consider the possibility that the rigid matrix may hinder the atomic motion necessary for inversion, or that it may provide a lattice-relaxation mechanism for rapidly deactivating an initially-formed excited *cis* or *trans* radical. If the isomer ratio *I*/*II* is thermodynamically controlled, the predominance of a single isomer even at 32°K would require at least a 15% difference in the total zero-point vibrational energies of *I* and *II* in the absence of a significant difference in the steric interactions of the matrix with the *cis* and *trans* radicals.[8] The fact that

objections can be raised to both kinetic and thermodynamic control of the I/II ratio suggests that the original interpretation of the ESR spectrum as indicative of only one isomer may need reexamination.

Several attempts have been made to determine the geometry at the α-carbon atom of the vinyl radical by comparing theoretically calculated spin densities for different configurations with the observed hyperfine splitting constants. Using a calculation based on the hyperconjugation theory of Coulson and Crawford,[11] Dixon calculated that the carbon-carbon-α-hydrogen bond angle θ (see structure III) lies between 120° and 150°.[12] Adrian and Karplus narrowed this range to 130° - 150° by using a valence bond calculation and by assuming that the 68 gauss splitting corresponds to the trans-β-proton.[13] However, the agreement of calculated and experimental hyperfine splittings for any value of θ may be fortuitous in this case; Strauss and Fraenkel have shown that the same type of valence bond method gives a poor fit between calculated and observed C^{13} hyperfine splittings.[14] An extended Hückel molecular orbital treatment by Petersen gives the best fit between theory and experiment for θ = 144°.[15]



III

RADICAL ADDITIONS TO SUBSTITUTED ACETYLENES

Alkenyl radicals have generally been assumed to be intermediates in free radical additions to alkynes. Radical additions to mono- and disubstituted acetylenes have been briefly discussed in several reviews concerned chiefly with radical additions to olefins.[16-18] The pertinence of individual stereochemical studies to the question of the configurational stability of alkenyl radicals must be carefully considered, since conclusive evidence for a homolytic mechanism is often lacking. Even in reactions for which a radical mechanism is established, free alkenyl radicals may not be involved. In several cases, interpretation of the results is complicated by incomplete product studies, ambiguous stereochemical assignments, and the absence of proof that product ratios are kinetically controlled.

A large number of radical additions to substituted acetylenes, most of which are initiated by peroxides or UV-irradiation, yield products corresponding to preferential trans addition to the triple bond. Included in this group are the liquid-phase addition of hydrogen bromide to propyne,[19,20] the bromination of 2-butynoic acid,[21] the addition of trichlorosilane to mono- and dialkylacetylenes,[22,23] the addition of alkyl- and arylthiols to ethoxyacetylene,[24] propiolic acid,[25,26] and arylacetylenes,[25,27,28] the reaction of thiolacetic acid with phenylacetylene[27] and 1-hexyne,[29] the addition of triphenyltin hydride to phenylacetylene,[30] and the addition of ditin and diarsine compounds to hexafluoro-2-butyne.[31] On the other hand, the brominations of several terminal and internal alkynes,[32-35] the reaction of hydrogen bromide with 1-bromoalkynes,[36] and the addition of perfluoroalkyl iodides to acetylenic compounds[37,38] appear to proceed predominantly by cis addition to the triple bond.

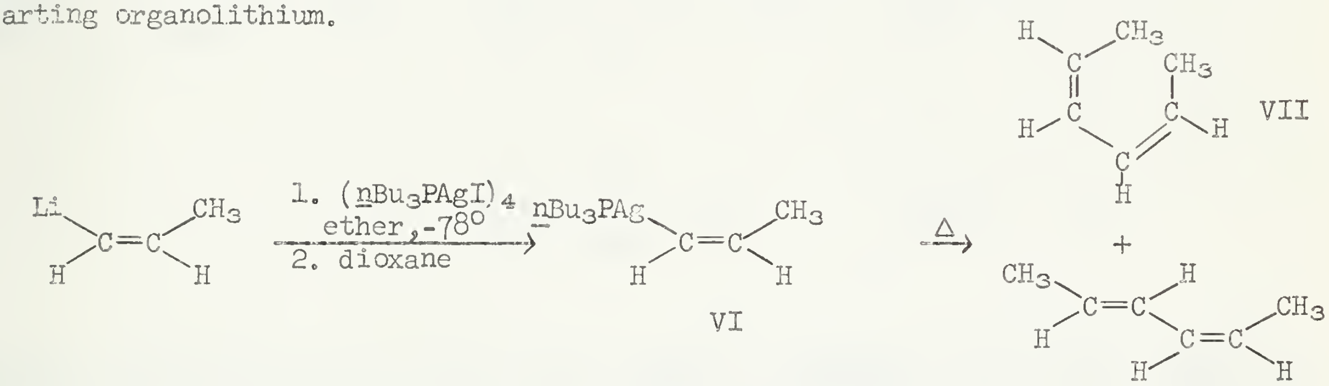
Skell and Allen have rationalized the exclusive trans UV-catalyzed hydrobromination of propyne in the liquid phase at -78° to -60° by 1) a configurationally stable cis alkenyl radical, 2) a bridged bromine radical, or 3) bromine atom addition to an initially-formed alkyne-hydrogen bromide complex, closely followed by hydrogen atom transfer.[19,20] Oswald, Griesbaum, Hudson, and Bregman have suggested that rapid equilibration of cis and trans alkenyl radicals and stereoselective hydrogen atom transfer to the less-hindered cis radical can account for the apparent trans addition of alkyl- and arylthiols to phenylacetylene.[27] Bergel'son has concluded that in the bromination of mono- and disubstituted acetylenes, the reaction stereochemistry is determined mostly by the relative thermodynamic stabilities of the cis and trans radicals, which in turn depend on the steric repulsions between the substituents on the radicals.[32,35] In contrast to this result, Truce, Klein, and Kruse have found that the steric requirements of the mesityl groups in the transition state of the product-forming step in the addition of 2-thiomesitylene to mesitylacetylene are not sufficiently large to reverse the normal trans stereochemistry of thiol addition.[28]

RADICAL REACTIONS OF ALKENYLMETALLIC COMPOUNDS

Beletskaya, Karpov, and Reutov have claimed a radical mechanism for the reaction of β-chlorovinylmercuric chloride with iodine in benzene and in carbon tetrachloride to form 1-iodo-2-chloroethylene.[39] They have also studied the stereochemistry of the β-bromostyrenes (IV) produced by the reaction of bromine with *cis* and *trans*-2-phenylethenylmercuric bromides (V).[40] In methanol in the presence of added bromide ion, the reaction proceeds with high (88.5%-*cis*; 93.5%-*trans*) retention of stereochemistry at the double bond. In carbon tetrachloride the reaction with either *cis* or *trans* V gives nearly equal amounts of *cis* and *trans*-β-bromostyrenes, as evidenced by the index of refraction of the distilled isomer mixture; the equilibrium *cis*/*trans* ratio is 3:7. If the reaction does indeed proceed by a radical mechanism and if the product-forming step is the bromination of a β-styrenyl radical, the similarity of the product ratios from *cis* and *trans* organomercurials indicates that the β-styrenyl radical either is linear or, if nonlinear, is rapidly inverting. In the latter case, the loss of original stereochemistry in the presence of as good a radical trap as molecular bromine requires that the isomerization be exceedingly rapid.

$$\underset{\text{V}}{\phi\text{CH=CH-HgBr}} + \text{Br}_2 \longrightarrow \underset{\text{IV}}{\phi\text{CH=CHBr}} + \text{HgBr}_2$$

Glockling has shown that the thermal decomposition of 1-(2-methylpropenyl)silver(I) in ethanol at -20° probably proceeds by a radical chain mechanism.[41] Whitesides and Casey have studied the thermal decompositions of *cis* and *trans*-1-propenyl- and 2-but-2-enylcopper(I) and silver(I) and the corresponding tri-*n*-butylphosphine complexes in ether at ambient temperatures.[42] The sole organic products are 2,4-hexadienes and 3,4-dimethyl-2,4-hexadienes, formed in high yields with greater than 99% retention of configuration at the double bond. For example, *cis*-1-propenyl(tri-*n*-butylphosphine)silver(I) (VI), prepared from 1-propenyllithium of 97% *cis* stereochemistry, gave *cis*,*cis*-2,4-hexadiene (VII) in 95% yield and *cis*,*trans*-2,4-hexadiene (VIII) in 4.8% yield, corresponding to a total yield of *cis* propenyl groups of 97% and a stereospecificity of 100%, based on the isomeric purity of the starting organolithium.



VIII

If free alkenyl radicals are formed in these reactions, product formation probably occurs by coupling of an alkenyl radical with a molecule of undecomposed organometallic, present in *ca* 0.1 M or lower concentration under the reaction conditions. In order to account for the high stereospecificity of diene formation, coupling must proceed at least 10^2 times faster than inversion of the radical:

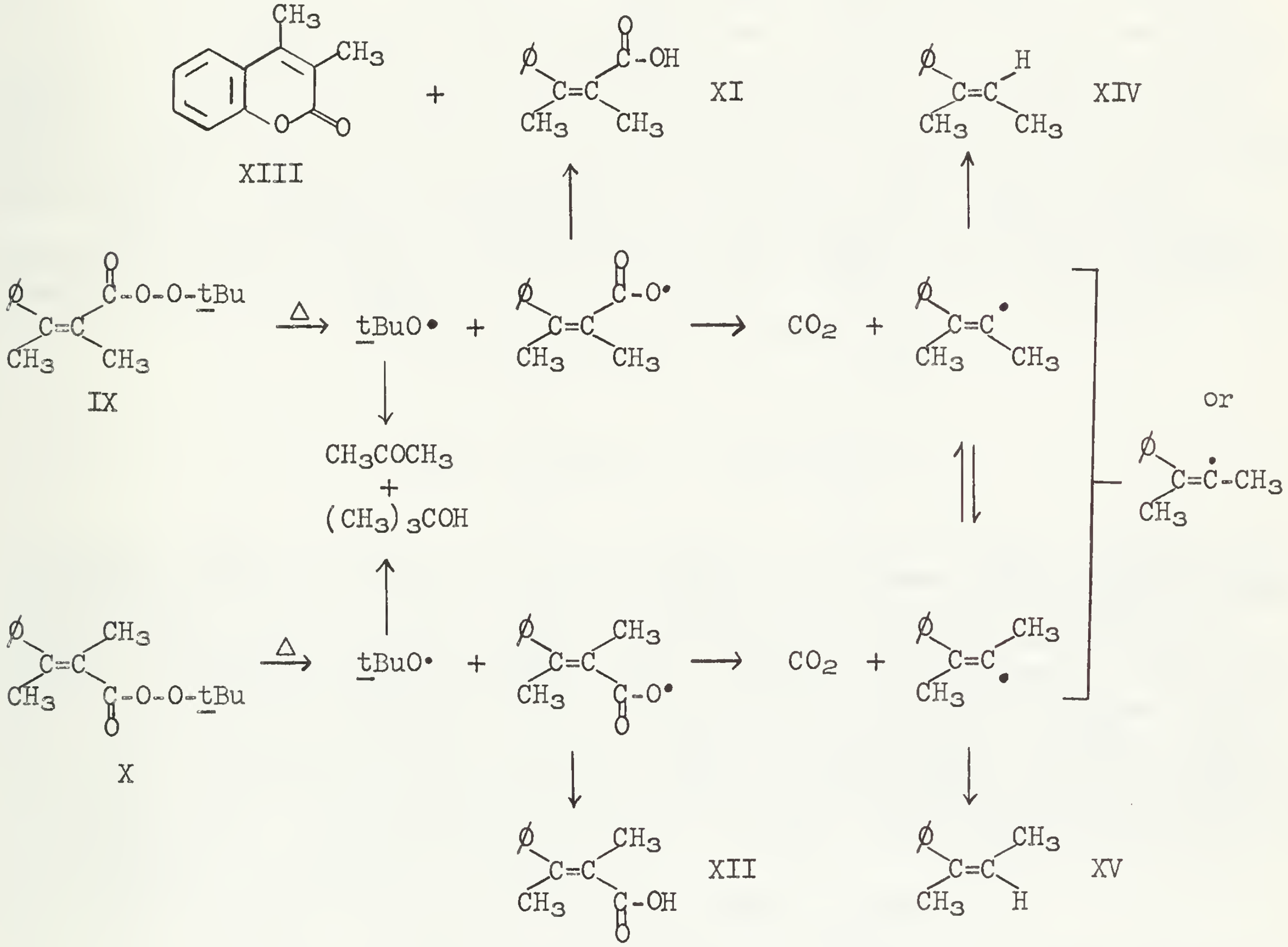
$$\text{k(coupling)} \times [\text{alkenyl radical}] \times [\text{alkenylmetallic}] > 10^2 \times \text{k(inversion)} \times [\text{alkenyl radical}]$$

If the configurational lifetime of the alkenyl radical is approximately that of the vinyl radical, on the order of 10^{-8} or 10^{-10} sec.,[4] then k(coupling) must be greater than 10^{11} l-mole^{-1}sec^{-1}. Whitesides and Casey argue that this minimum value for

k(coupling) is unreasonably large and conclude that the reaction does not proceed with the formation of free alkenyl radicals. They also rule out geminate combination of radicals within a solvent cage because they feel that the 100% efficiency of cage combination necessary to explain the product yields is unlikely. They do not exclude the possibility that alkenyl radicals are formed which are configurationally stabilized by *π*-complexation to the metal atoms.

GENERATION OF ALKENYL RADICALS BY PERESTER DECOMPOSITION

Bartlett has proposed a nonconcerted radical mechanism, in which the initial step is cleavage of an oxygen-oxygen bond, for the thermal decomposition of *tert*-butyl percinnamate.[43] Kampmeier and Fantazier decomposed *tert*-butyl *cis* and *trans*-*α*,*β*-dimethylpercinnamates (*IX* and *X*) in cumene at 110°.[44] The observed products are consistent with the following reaction scheme:



Dicumyl is also produced in significant (*cis*-43.4%; *trans*-63.5%) yields. *cis* and *trans*-*α*,*β*-Dimethylcinnamic acids (*XI* and *XII*) are obtained in low (1-2%) yields and have the same stereochemistry as the parent perester. 3,4-Dimethylcoumarin (*XIII*) is formed exclusively from the *cis* perester in 12.8% yield. If the acids and the coumarin arise through the acyloxy radicals rather than by a minor heterolytic pathway, these observations indicate that the *cis* and *trans* acyloxy radicals do not interconvert.

In separate experiments, Kampmeier and Fantazier showed that *trans* perester (*X*) recovered after partial decomposition contains no *cis* perester (*IX*), that *cis* and *trans*-*α*,*β*-dimethylcinnamic acids added to decomposing *trans* perester are recovered nearly quantitatively and unisomerized, and that *cis* and *trans*-2-phenyl-2-butenes (*XIV* and *XV*) are not isomerized under the reaction conditions. The sum of the yields of *cis* and *trans*-2-phenyl-2-butenes accounts for most of the alkenyl radicals formed, as measured by the evolution of carbon dioxide, so that hydrogen abstraction is the major reaction of the alkenyl radicals. The *cis* and *trans*

peresters give mixtures of olefins XIV and XV with the same *cis/trans* ratios, 1.1-1.2. At 100° the equilibrium *cis/trans* ratio is approximately four.[45] The common kinetically-controlled isomer ratio again supports the intermediacy of a linear or rapidly-inverting nonlinear radical.

If nonlinear alkenyl radicals are stereospecifically generated from the *cis* and *trans* peresters, it might be possible to trap the radicals with an efficient scavenger before they can isomerize. The first-order rate constant for decomposition of the *trans* perester is not affected by the addition of an equimolar quantity of 2-thiomesitylene, even though the yield of *trans*-α,β-dimethylcinnamic acid increases from 1.9% to 36.3%.[46] This result requires separate product- and rate-determining steps and suggests that Bartlett's one-bond cleavage mechanism[43] is also operating in this case. As the concentration of added 2-thiomesitylene is increased, the *cis/trans* ratio of 2-phenyl-2-butenes from *both cis* and *trans* peresters increases toward the equilibrium value. The failure of the thiol to trap a mixture of radicals richer in the *trans* isomer from the *trans* perester does not rule out the stereospecific formation of nonlinear radicals, since isomerization of the olefinic products by the added thiol would obscure this observation. A precedent for such olefin isomerization is found in the work of Oswald, Griesbaum, Hudson, and Bregman,[27] who found that ethanethiol and thiophenol catalyze the isomerization of *cis*-β-thiophenylstyrene and *cis*-β-thioethylstyrene to the more stable *trans* isomers.

Singer and Kong have investigated the thermal decomposition of the *tert*-butyl peresters of *cis* and *trans*-α-methylcinnamic acids (XVI) and of *cis* and *trans*-α-phenylcinnamic acids (XVII) in several solvents at 110°.[47,48] In a single solvent,

$$\phi CH{=}C(CH_3)CO_3\underline{t}Bu \xrightarrow{\Delta} \phi CH{=}CHCH_3$$

XVI XVIII

$$\phi CH{=}C(\phi)CO_3\underline{t}Bu \xrightarrow{\Delta} \phi CH{=}CH\phi$$

XVII XIX

the *cis* and *trans* peresters give the same kinetically-controlled (nonequilibrium) *cis/trans* ratios of 1-propenylbenzenes (XVIII) or stilbenes (XIX); the *cis/trans* olefin ratios increase as the solvent is changed from toluene to cyclohexene to cumene. The authors interpret these results in terms of stereoselective capture of rapidly-equilibrating *cis* and *trans* alkenyl radicals by the solvent. Cumene has the largest steric requirement in the transition state for hydrogen atom transfer, so that this solvent shows the greatest preference for hydrogen transfer *trans* to the α-phenyl group and yields an olefin mixture containing the greatest proportion of the *cis* isomer. Similar reasoning has been used to explain the variation of the *cis/trans* decalin ratios observed when *cis* or *trans*-9-carbo-*tert*-butylperoxydecalin is decomposed in different solvents.[49]

GENERATION OF ALKENYL RADICALS BY THE HUNSDIECKER REACTION

The brominative decarboxylation of the silver salts of carboxylic acids is regarded as a reliable method for generating alkyl radicals.[50] Berman and Price have reported that the bromination of silver *cis* and *trans*-cinnamates in refluxing carbon tetrachloride gives *trans*-β-bromostyrene (10% and 17.5%, respectively), 1,1,2-tribromo-2-phenylethane (25% and 35%), and the cinnamic acid of unchanged stereochemistry (12% and 8%).[51] Since at equilibrium β-bromostyrene contains an appreciable amount of the *cis* isomer,[40] the exclusive formation of the *trans* isomer from both *cis* and *trans* silver salts indicates that the free energy of the transition state for bromination of the *cis* radical is significantly (>3.2 kcal/mole if 1% of *cis*-β-bromostyrene could have been detected) higher than that of the *trans* radical. If the thermodynamic stabilities of the *cis* and *trans* radicals are comparable, this explanation corresponds to a high stereoselectivity for bromine transfer to the intermediate vinyl radical. Conclusions drawn from this study must be regarded as tentative, since large percentages of starting silver salts were not accounted for.

The Hunsdiecker reactions of silver *cis* and *trans*-α-phenylcinnamates give different *cis/trans* ratios of α-bromostilbenes.[52] Studies of product stabilities under the reaction conditions are not reported.

GENERATION OF ALKENYL RADICALS BY THERMAL DECOMPOSITION OF DIACYL PEROXIDES

Simamura, Tokumaru, and Yui decomposed *cis* and *trans*-dicinnamyl peroxides in carbon tetrachloride and in bromotrichloromethane.[53] The stereochemistry of the *β*-halostyrene products is given below:

isomer of peroxide	solvent	*cis*/*trans* ratio of product ØCH=CHCl	ØCH=CHBr
cis	CCl_4	18/82	
	$BrCCl_3$		27/73
trans	CCl_4	19/81	
	$BrCCl_3$		14/86

Separate experiments showed that the *β*-halostyrenes are not isomerized under the reaction conditions.

A common linear intermediate radical is ruled out as the *sole* source of products by the different *cis*/*trans* ratios from *cis* and *trans* peroxides in bromotrichloromethane. The partial retention of configuration in bromotrichloromethane but not in carbon tetrachloride is consistent with a competition between inversion of stereospecifically-generated alkenyl radicals and trapping of the radicals by solvent; the smaller activation energy requirement for breaking a bromine-carbon bond in the chain transfer step is reflected in the greater ease with which bromotrichloromethane adds to olefins.[54] In carbon tetrachloride the equilibration of the isomeric alkenyl radicals is complete; if the equilibrium constant for the radical isomerization is near unity, the 1:4 *cis*/*trans* product isomer ratio suggests that the phenyl group may sterically hinder halogen transfer to the *cis* radical.

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ISOMERIZATION OF ORGANIC THIOCYANATES TO ISOTHIOCYANATES

Reported by Joseph C. Stickler March 2, 1967

INTRODUCTION

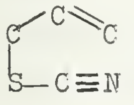
The observation that organic thiocyanates isomerize to isothiocyanates (equation 1) was made about a century ago.[1,2] However, not until this decade

$$R-\overline{\underline{S}}-C\equiv N| \longrightarrow R-\overline{N}=C=S\rangle \qquad (1)$$

have serious investigations been initiated to obtain a mechanistic description of these isomerizations. Experimental evidence in these investigations has indicated that they may proceed by at least four pathways depending upon the structure of the organic substrate and reaction conditions. If the organic moiety contains an allylic double bond, the reaction may proceed by a shift in that bond and a change in the site of anion attachment.[3-6] Also, conditions can be controlled so that either a direct displacement[7] or ionization mechanism[8] is responsible for the isomerization of saturated systems. The isomerization of thiocyanates upon irradiation is believed to proceed by a radical pathway.[9] An interesting outgrowth of these isomerization studies was the information they yielded on the ambident reactivity of the thiocyanate anion.[7]

ALLYLIC SYSTEMS

The isomerization of allylic thiocyanates to isothiocyanates has been known since 1875.[1,2] The fact that the site of attachment to the organic substrate changed in allylic isomerization was substantiated when it was demonstrated that crotyl thiocyanate upon heating to 140° yielded quantitatively α-methylallyl isothiocyanate.[4] The proposed mechanism for this rearrangement contains a six-membered-ring transition state, which may be represented by contributing structures I through IV or alternatively by V. This is a characterization similar to that attributed to the rearrangement of α,α-dimethylallyl chloride by Young, Winstein and Goering.[10]



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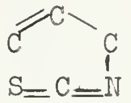

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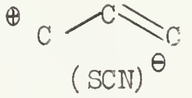

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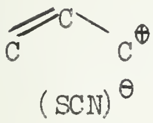
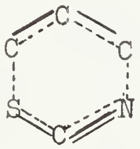


IV



V

This mechanism is supported by several experimental considerations. The entropy of activation for the allyl and 2-methylallyl thiocyanate rearrangement are -9.4 ± 1 and -8.7 ± 1 cal./deg.-mole[6] respectively which is indicative of a high degree of order in the transition state relative to the ground state. These values are the same sign and order of magnitude as several reactions believed to proceed through a six-membered-ring transition state such as the Claisen rearrangement of allyl vinyl ether.[11] These rearrangements obey first-order

kinetics. The rate of conversion in the allylic case is faster than in the saturated case. For instance, allyl thiocyanate[6] in toluene at 86.4° isomerizes at a rate of 3.81×10^{-4} sec^{-1} as compared to 1.87×10^{-6} sec^{-1} for benzhydryl thiocyanate at 90.0° in benzene.[8] The smallness of charge separation in the transition state is indicated by the fact that neither changes in solvents towards greater polarity nor added salts increased the rate of reaction significantly. The changes in rate appear especially small when compared to the data compiled by Streitwieser[12] for the solvolysis of other allylic systems believed to occur by way of an ionization route. For instance, for the solvolysis of γ,γ-dimethylallyl chloride, the ratio $k_{50\%\ \mathrm{ethanol}}:k_{\mathrm{ethanol}} = 3300$, but for the isomerization of the corresponding thiocyanate,[5] $k_{\mathrm{acetonitrile}}:k_{\mathrm{cyclohexane}} = 3$. Thus the contributions of structures III and IV are believed to be small compared to I and II, with V perhaps being the best representation.

Although the isomerization of a pure isothiocyanate to thiocyanate has not been clearly established, it is known that an equilibrium state is obtained in the isomerization of allylic thiocyanates.[5,13,14] From the results of these equilibria in Table I, several points of interest have been made.

TABLE I[5]

Equilibrium thiocyanate/isothiocyanate at 100° in different media.

Compound	% of thiocyanate at equilibrium[a]			Conc. m/l
	Pure	cyclohexane	acetonitrile	
Benzhydryl	-	<1	2-3	0.1-0.75
allyl	<1	<1	9-11	10^{-3}-10^{-1}
γ-methylallyl	11	5	27	10^{-3}
γ,γ-dimethylallyl	40	18	50	10^{-3}

[a] Analysis by U.V. and I.R. spectrophotometry.

As the polarity of the medium is increased, the percent of thiocyanate increases, which is consistent with the fact that the thiocyanate has a higher dipole moment and therefore would be more stable in a polar solvent. If the rearrangement causes the organic substrate to lose stability by loss of hyperconjugative stabilization of a γ-methyl group, then there is a greater amount of the thiocyanate in equilibrium. Contrasting with this result is the fact that the more methyl substitution at the gamma position, the faster the rate of conversion to the isothiocyanate as seen from Table II. Apparently the greater the ability of the organic substrate to stabilize a positive charge the more contribution the ionic structures III and IV make to the transition state. In what can apparently be considered an extreme case of the equilibrium favoring the thiocyanate, γ-phenylallylthiocyanate does not rearrange at all with an allylic shift to α-phenylallyl isothiocyanate which would no longer have the allylic double bond conjugated to the phenyl group, but instead isomerizes to γ-phenylallyl isothiocyanate.[15] The mechanism believed to be responsible is the same as that involved in the isomerization of saturated thiocyanates and will be discussed in the next section.

TABLE II[5]

First-order rate coefficients[a] at 60° for the isomeric rearrangement of allylic thiocyanates:

$$RR'C{=}CHCH_2SCN \longrightarrow RR'C(NCS)\underset{H}{C}{=}CH_2$$

Compound		$10^5\ k_{60^\circ}(sec^{-1})$		$(k_A/k_C)_{60^\circ}$
R	R'	A[b]	C[b]	
H	H	1.8	3.3	0.5
CH_3[c]	H	27	31	0.9
CH_3	CH_3	270[d]	96[d]	3

[a] Determined by U.V. spectrophotometry.

[b] A and C stand for acetonitrile and cyclohexane solvents respectively.

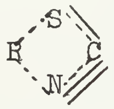
[c] trans

[d] Extrapolated from lower temperature data.

SATURATED SYSTEMS

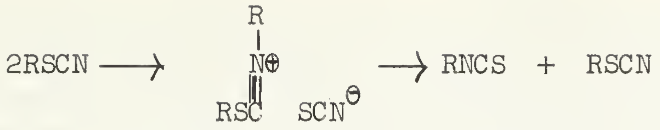
Many saturated thiocyanates are known to isomerize to the corresponding isothiocyanates. The mechanism believed to apply to most of these systems is a unimolecular ionization to an ion pair, which can return to starting material or go to the isothiocyanate. Before considering the details of the above mechanistic description, the experimental evidence which excludes other pathways of reasonable a priori probability will be presented.

The likelihood of a concerted pathway in which there would be some bond making of the nitrogen to the α-carbon before complete bond breaking of the sulfur to α-carbon bond seems small. This route would involve a four-membered-ring transition state as shown in equation (2) and would be analogous to the Chapman rearrangement of imino esters.[16] Such a transition state would probably

$R{-}S{-}C{\equiv}N \longrightarrow$  $\longrightarrow R{-}N{=}C{=}S$ (2)

have a higher energy of activation than the allylic isomerization; however, the energies of activation for saturated and allylic systems are quite similar. Also, one might expect retention of optical purity, but extensive racemization is found when an optically active substrate is employed.[17] The argument that the geometry of the C-S-C≡N group is prohibitive to the concerted mechanism has been made.[8]

A possible second route is represented by equation (3). This route is discredited by the fact that the kinetics are first order.



$$2RSCN \longrightarrow \overset{\displaystyle R}{\underset{\displaystyle RSC}{N^{\oplus}}}\ SCN^{\ominus} \longrightarrow RNCS + RSCN \tag{3}$$

Again, one would expect retention of optical purity in the product, which is not found.

A third pathway might be an α-elimination to a carbene and thiocyanic acid, and then recombination. However, attempts to identify the acid by spectroscopy and to trap a carbene failed.[6]

A fourth possible mechanism would be homolytic cleavage followed by simple recombination (equation 4) which would yield the necessary first-order kinetics, but the more likely chain process would result in a more complicated expression.

$$R\text{-}SCN \longrightarrow R\cdot + \cdot SCN \longrightarrow R\text{-}NCS \tag{4}$$

Besides the solvent and salt effect which are more indicative of an ionization mechanism, no side products were isolated which would be expected to accompany a radical pathway. However, it appears that conditions can be controlled so as to lead to an isomerization of benzyl and benzhydryl thiocyanates to the isothiocyanates by a radical pathway. Mazzucato[9] recently reported that when benzyl thiocyanate is irradiated with a low pressure mercury arc, using the 2537 Å line, at a concentration of about 10^{-4}M in n-hexane, at room temperature and with the exclusion of oxygen from the system, a photoequilibrium with the isothiocyanate was established. The photostationary equilibrium mixture was about 70% thiocyanate and 30% isothiocyanate. On the basis of detection of the fluorescence emission of the benzyl radical in the 460-530mμ region starting from both the thio- and isothiocyanate in low temperature photolyses, a radical mechanism was suggested.

Having disposed of the above pathways, evidence supporting the ionization mechanism will be presented. Perhaps the most persuasive evidence is the comparison of this system to the many similar systems studied by Winstein,[18] Smith,[19] Goering,[20] Darwish[21] and others. The proposed mechanism is an ionization to form an ion pair intermediate through which isomerization occurs. The evidence overwhelmingly points toward this pathway and the purpose here will be to see how well a detailed picture of this mechanism is fulfilled. As a point of reference, equations (5) and (6) representing the detailed process of ionization-dissociation described by Winstein and coworkers[22] will be employed. Several

$$I \xrightarrow{\text{ionization}} \underset{\substack{\text{intimate}\\ \text{or}\\ \text{internal}\\ \text{ion pair}}}{II} \longrightarrow \underset{\substack{\text{external}\\ \text{or}\\ \text{solvent-}\\ \text{separated}\\ \text{ion pair}}}{III} \xrightarrow{\text{dissociation}} \underset{\substack{\text{dissociated}\\ \text{ions}}}{IV} \tag{5}$$

$$RX \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} R^+X^- \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} R^+\|X^- \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} R^+ + X^- \tag{6}$$

types of organic substrates have been studied, but because of its suitability for extensive studies attention was mainly focused on the benzhydryl substrate.

As previously stated, the reaction obeys first-order kinetics. The energy and entropy of activation for the isomerization of 4,4'-dimethylbenzhydryl thiocyanate in acetonitrile are 20.67 kcal./mole and -10.0 cal./mole-deg., respectively.[8]

In a study of solvent effects on the rate of isomerization, Fava and coworkers demonstrated that an increase in polarity accelerated the rate, which is compatible with the ionization mechanism. For example, at 90° for the benzhydryl case, the rates in methyl ethyl ketone, acetonitrile and dimethylformamide relative to benzene were 10, 150 and 280. This solvent sensitivity is similar in order of magnitude to that of other reactions believed to occur by a unimolecular ionization. For instance, the ratio of rates in acetonitrile and benzene are 120 for the rearrangement of camphene hydrochloride and 28 for the rearrangement of 9-decalyl perbenzoate.[8]

The effect of structure on reactivity revealed that with increasing stability of the carbonium ion formed by ionization, the rate of isomerization also increased. A qualitative study of the rates of the series n-butyl, sec-butyl, and t-butyl thiocyanates indicated that rate increased in going toward the more highly branched substrate.[6] In a study of para-substituted benzhydryl thiocyanates, Fava and coworkers demonstrated that electron releasing substituents facilitated the rate, while electron withdrawing groups hindered the rate. Using Brown's σ^+ values[23] a Hammett plot of log k/k_o vs. σ^+ resulted in a linear relationship with $\rho = -3.40$ in acetonitrile at 70°. This result compares well with $\rho = -4.05$ for the solvolysis of benzhydryl chloride in ethanol.[8] Hence structural modifications of the organic moiety which aid the stabilization of a positive charge increases the rate of isomerization.

Salts added to the reaction medium also increased the rate of isomerization, thus supporting the ionization mechanism. Fava and coworkers[8] investigated in particular the effects of two salts, sodium perchlorate and sodium thiocyanate. The investigation was carried out in two solvents, methyl ethyl ketone and acetonitrile; the effect being greater in the less polar methyl ethyl ketone. The results fit well the Winstein equation[24](7) for "normal" salt

$$k = k_o\,(1 + b\,[\text{salt}]) \tag{7}$$

effects. The b values are summarized in Table III. The possibility that a concurrent direct displacement by the nitrogen end of the ionic thiocyanate might account for its greater effect as compared with the sodium perchlorate was not completely ruled out. However, the ratio of the b values in the two solvents was independent of the salt, which is expected if the effect is a specific salt effect. Also, the degree of specificity of the different salts is not uncommon.[8]

TABLE III

Salt effects on isomerization of benzhydryl thiocyanate at 90° in different media.

	b values from Winstein equation (7)		
Salt	Methyl ethyl ketone	Acetonitrile	$\frac{b_{MeEtCO}}{b_{MeCN}}$
NaSCN	16.7	4.27	3.92
$NaClO_4$	11.7	2.93	3.99

Although the solvent, structural, and the salt effects described above lead strongly to the conclusion that an ionization pathway is operative, they do not give a detailed picture of the mechanism. Fava and coworkers further particularized

the mechanism by performing exchange experiments with sulfur labeled sodium thiocyanate.[8,25] The main portion of these exchange experiments was carried out on the 4,4'-dimethylbenzhydryl thiocyanate where it was shown that direct displacement by either the sulfur or nitrogen end of the ionic thiocyanate on the organic substrate is negligible (equations 8 and 9), since the kinetics indicated

$$^{-}NCS^{*} + RSCN \rightleftharpoons NCS^{*}R + SCN^{-} \qquad (8)$$

$$^{*}SCN^{-} + RSCN \rightleftharpoons {}^{*}SCNR + SCN^{-} \qquad (9)$$

essentially unimolecular exchange with ionic thiocyanate. Therefore all radioactivity must enter the organic substrate by way of the ionization route. The first conclusion drawn from these experiments was that since the amount of label on the ionic thiocyanate always remained far greater than that on the organic thiocyanate or isothiocyanate, the organic thiocyanate could not have become completely dissociated upon ionization or the labeled ionic thiocyanate would have become equilibrated with the organic thiocyanate. Thus it was proposed that the isomerization occurred through an ion pair.

The salt effect on both the rate of isomerization and exchange of 4,4'-dimethylbenzhydryl thiocyanate in acetonitrile at 25° were examined. The results are shown in Table IV. As can be seen from Table IV the rate of exchange is more greatly effected by added salts than the isomerization rate. The author interpreted this to mean that a more advanced degree of ionization (i.e. greater charge separation) was involved in exchange than in isomerization. Further indication that exchange occurs at a more advanced stage of ionization is the ρ value of -4.5 for exchange at 70° in acetonitrile.[26] This is more negative than the ρ = -3.40 measured under the same conditions for isomerization indicating a more highly polar transition state. Whether exchange might occur at the external ion pair or upon dissociation or both cannot be determined from this data. However, the authors have speculated that for the highly polar acetonitrile and the benzhydryl moiety, the dissociated carbonium ion seems the more probable intermediate for the first-order exchange process. Assuming that isomerization occurs at the internal ion pair stage, and that if in some instances the ionization proceeds further and exchange takes place with labeled ionic thiocyanate, then these exchanged species will proceed back to the internal ion pair and then partition between thiocyanate and isothiocyanate, more information may be obtained. The ratio of incorporated label in thiocyanate and isothiocyanate was made and it was determined that the ion pair returned to covalency with the sulfur end five times more often than the nitrogen end. With this information a lower

TABLE IV

Salt effects on rates of exchange and isomerization of 4,4'-dimethylbenzhydryl thiocyanate in acetonitrile

	b values from Winstein equation (7)	
	Isomerization[a]	Exchange[b]
$NaClO_4$	2	38
NaSCN	4	48

[a] 25.0 ± 0.1°

[b] 0.2 ± 0.1°

limit may be set on the rate of ionization by the expression (10) where k_1 is the rate of ionization and k_{is} the isomerization rate. The determination

$$k_1 = \frac{k_S + k_N}{k_N} k_{is} = 6k_{is} \tag{10}$$

of the rate of ionization in this manner assumes that the ion-pair stage at which isomerization occurs is not preceded by another ion pair which returns exclusively to the thiocyanate. The stereochemical evidence indicated that racemization of p-chlorobenzhydryl thiocyanate and isomerization takes place at the same intermediate, thus supporting the assumption that no ion pair precedes the ion pair stage responsible for isomerization.[17,26] This method is similar to that employed by Goering and coworkers in their study of the p-nitrobenzoate-carbonyl -O^{18} system,[20] the main exception being that partition between the isotopic oxygens is not dependent upon reaction conditions as is the ratio k_S/k_N.

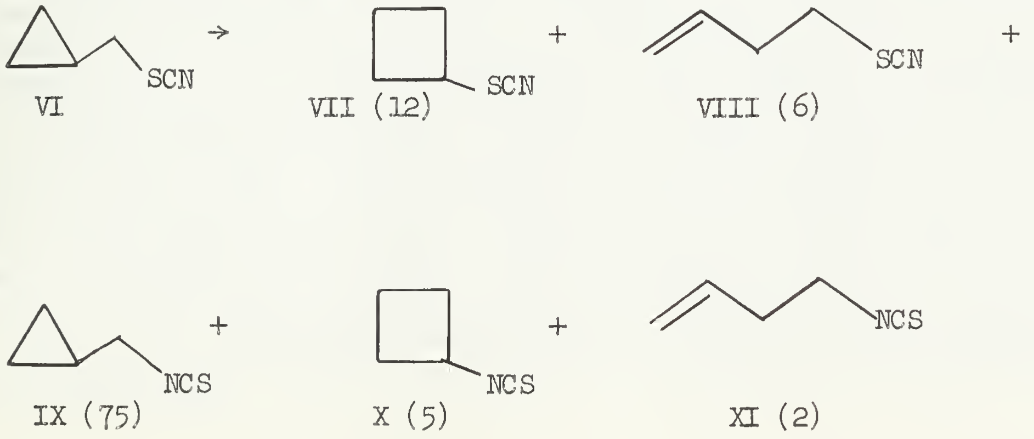
From the ratio of the rate of exchange to the rate of ionization (equation 11), it is possible to calculate an upper limit to the percent of dissociation that occurs. Using 4,4'-dimethylbenzhydryl thiocyanate in acetonitrile at 0° with 0.01M NaSCN,

$$\frac{k_{ex}}{k_{is}} \Bigg/ \frac{k_S + k_N}{k_N} \tag{11}$$

the upper limit is calculated to be 5.3%. The authors make the following summary to the result: Out of 100 internal ion pairs formed, about 5 undergo further ionization and 95 return to the covalent state. From the partition data mentioned above it was concluded that of the 95 returning to covalency, about 79 return to thiocyanate and 16 to the isothiocyanate. Also concluded was that under conditions favoring ionization to a smaller extent (less polar solvent or less stable carbonium ion), return to covalency from the internal ion pair predominates even more completely.

An outgrowth of these exchange experiments employed to particularize the isomerization mechanism was an extensive mechanistic study on the isotopic exchange between substituted benzhydryl thiocyanates and ionic thiocyanates. Fava and coworkers[26,27] concluded that with strongly electron attracting substituents a bimolecular pathway prevailed and with strongly electron donating substituents a unimolecular process was obtained. However, with substituents having intermediate electron-donating abilities, concurrent bimolecular and unimolecular mechanisms were operative.

The isomerization of cyclopropylcarbinyl thiocyanate (VI) is of special interest, since this is the only example known in which the saturated organic moiety undergoes a rearrangement of the carbon skeleton during isomerization. Spurlock and Newallis[28] have reported that the isomerization of cyclopropylcarbinyl thiocyanate at 155°C in acetonitrile yielded compounds VII through XI, the respective percent yield indicated below each structure. The kinetics were



VI VII (12) VIII (6)

IX (75) X (5) XI (2)

first order and the rate of isomerization at 154.7° was 2.55×10^{-5} sec^{-1} in dimethylformamide. The authors have reported that control experiments indicated each of the products VII-XI was stable to the reaction conditions. In the presence of added potassium thiocyanate in dimethylformamide solutions, the isomerization rate was increased, but the products and their distribution were unaffected. Since direct displacement by the ionic thiocyanate would favor the cyclopropylcarbinyl isothiocyanate, the authors concluded that the acceleration of the rate could be attributed mainly to "normal" salt effects.

The isomerization of methyl thiocyanate is somewhat unexpected since experiments have indicated that isomerization of n-butyl thiocyanate is negligible. However, at 131°, the boiling point of methyl thiocyanate, it isomerized and was aided by dissolved salts.[29] Although the isomerization proceeds in the neat methyl thiocyanate, it is prevented in non-polar solvents.[6] The kinetics, which were measured in the pure state, were found to fit a first-order rate law; and the rate of isomerization at 120° was 1.02×10^{-7} sec^{-1}. From the above rate data, an energy and entropy of activation were calculated to be 41 kcal./mole and 31 cal./mole-deg., respectively.[30] The concerted four-membered ring,[30] bimolecular[6] and ionization[10] mechanisms have all been suggested on the basis of this sparse experimental data. A more systematic and comprehensive study of this system seems to be necessary for classification of the mechanism involved.

AMBIDENT NATURE OF THE THIOCYANATE ANION

One of the interesting aspects of the isomerization studies is the information they yield about the ambident reactivity of the thiocyanate anion. So far we have seen that there are three general mechanisms by which these isomerizations proceed; by allylic rearrangement, ionization and radical pathways. In order to provide further scope to the study of this ambident reactivity, Fava and coworkers[7] were able to control the conditions of the isomerization so as to provide the isomerization with another quite general pathway. By using the benzyl substrate which undergoes direct substitution easily and maintaining a substantial amount of ionic thiocyanate in the reaction media, the isomerization was found to proceed mainly by an S_N2 mechanism. Radioactive thiocyanate was employed and the rates of exchange, which proceeded either by a direct displacement of the S or N end of ionic thiocyanate as well as the rate of isomerization, direct displacement by the N end, were measured. Since the rate of isomerization was on the order of 10^{-6} and the isotopic exchange rate on the order of 10^{-4}, the rate of exchange is approximately equal to the reactivity of the sulfur end. The rate of isomerization is equal to the reactivity of the nitrogen end of the thiocyanate anion. Therefore the ratio of k_{ex}/k_{is} equals the reactivity ratio k_S/k_N. In acetonitrile and methyl ethyl ketone at temperatures ranging from 70-100°, the values of k_S/k_N were on the order of 10^2 to 10^3 for the benzyl substrate. For instance, at 70° the ratios of k_S/k_N are 1000 and 725 for the methyl ethyl ketone and acetonitrile respectively; while values of 650 and 460 are obtained at 100° for the same two solvents. On the other hand, in reactions studied by Cannell and Taft[31] in which carbonium ions were generated in aqueous solutions independently from the thiocyanate ions, k_S/k_N values ranging from 2 to 9 were determined from product ratios. In Fava's work[25] concerned with the isomerization by the ionization mechanism, a value for k_S/k_N of 5 was obtained for the isomerization of 4,4'-dimethylbenzhydryl thiocyanate in acetonitrile, which is on the same order of magnitude as values obtained from the Cannell and Taft work.

As indicated from the above results, this system provides a good method for determining how various factors affect the relative reactivities of the two ends of the thiocyanate anion. Further investigation into the solvent effects on this ambident anion might prove useful in ascertaining the role solvation plays in determining relative reactivities. Also a systematic study of the thiocyanate radical, in cases where the radical pathway is operative, could reveal more about the nature of the relative reactivity of the two ends of the thiocyanate radical. An extensive review related to nucleophilic ambifunctional reactivity by Gompper[32] has been published.

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THE PHYSIOLOGICALLY ACTIVE CONSTITUENTS OF MARIHUANA

Reported by Donald C. Schlegel March 6, 1967

INTRODUCTION

Cannabis sativa Linn., more commonly known as hemp, is a plant which grows wild or is cultivated throughout much of the world. The greenish resin known as marihuana (The Americas), hashish (Middle East), or charas (Far East) can be extracted from the flowers and seeds of the female plant and the leaves of both sexes.[1] The oil is composed of at least 25 recognized compounds, the major constituents being caryophyllene 45.7%, β-humulene 16%, α-selinene 8.6%, β-farnesene 5.1%, α-bergamotene 5%, β-phellandrene 2.7%.[2] In smaller content, 1.2% or less depending on the geographical origin, are two tetrahydrocannabinols, the active constituents which make marihuana a psychotomimetically active drug.[3] The search for these compounds, their structural elucidation and most recently the resynthesis of their optically inactive forms are the topics of this seminar.

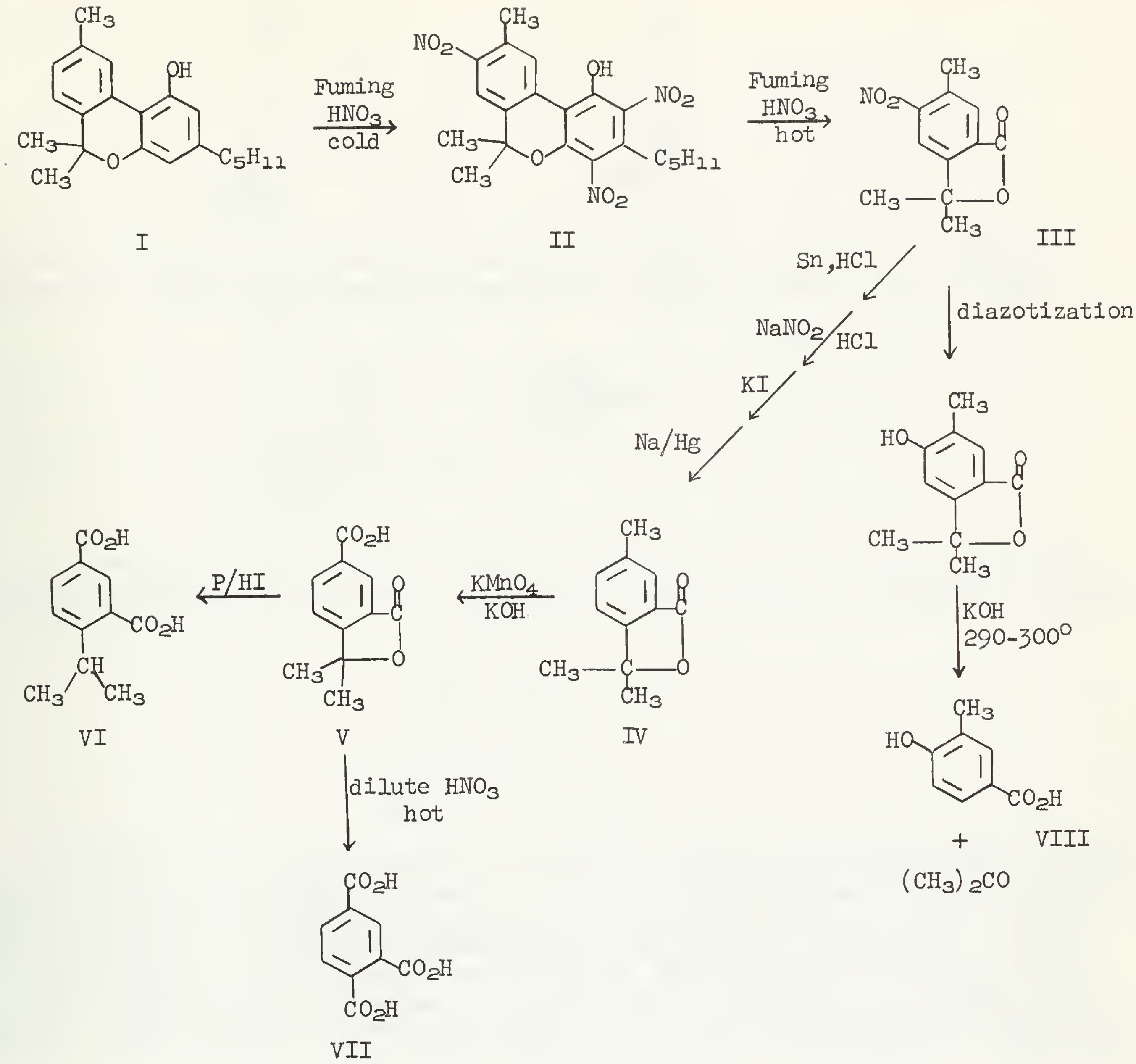
PHYSIOLOGICAL EFFECTS

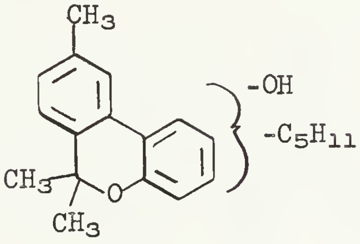
Marihuana is a psychotomimetically active drug. It is known to have a profound effect on the central nervous system. It can be taken into the body by smoking or direct ingestion. The effects have been "described as a feeling of well being alternating with depression, distortions of time and space, and double consciousness."[1] Illusion and fanciful hallucinations are common and disorientation and delirium may follow. An increased sensitivity of the eyes to light is also observed.[4]

STRUCTURE ELUCIDATION

In the 1870's, chemists initially began to investigate marihuana.[5] They met with little success, however, and it wasn't until the 1890's and the work of Wood, Spivey and Easterfield[5] that much was known about the supposedly active constituent or constituents of marihuana. At that time they isolated a material $C_{21}H_{26}O_2$, I, from the higher boiling fraction of the marihuana resin. Treatment of this compound with cold fuming nitric acid yielded a yellow trinitro derivative $C_{21}H_{23}N_3O_8$, II. Further oxidation of this product with hot fuming nitric acid gave among other products a mononitro derivative $C_{11}H_{11}NO_4$, III. The nitro group was reduced to the amine, diazotized, treated with potassium iodide to form the iodide and then reduced with sodium amalgum to form $C_{11}H_{12}O_2$, IV, called cannabinolactone. This material was reoxidized with basic permanganate to give a $C_{11}H_{10}O_4$ compound, V, cannabinolactonic acid. Reduction of this gave a dibasic acid $C_{11}H_{12}O_4$, VI. Thirty years later Cahn[6] further oxidized cannabinolactonic acid with hot dilute nitric acid and obtained trimellitic acid, VII, thus showing the aromatic ring substitution. He also demonstrated that the acid formed a lactone with a tertiary alcohol by collecting acetone and 3-hydroxy-4-methylbenzoic acid, VIII, on potassium hydroxide cleavage of hydroxy-cannabinolactone.

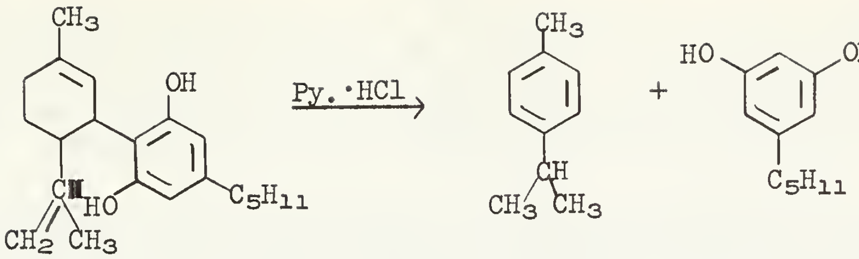
Cahn applied the name cannabinol, earlier used to denote the high boiling fraction of marihuana, to the compound $C_{21}H_{26}O_2$, I. The material formed both monomethyl ether and monoacetyl derivatives. Measurement of the critical oxidation potential gave a value, $E_c = 0.995 \pm 0.10$, characteristic of substituted phenols but not carbinols. Recovery of [illegible]hexanoic acid on potassium permanganate oxidation indicated the presence of a straight chain moiety. Empirical formula considerations suggested that the chain was a n-pentyl side chain on the phenolic ring with the sixth carbon atom coming from oxidation of the ring. Assembling the information gave IX as the basic structure for cannabinol. It was not until the general structure of cannabidiol was determined by groups led by Todd and Adams that the complete structure of cannabinol was known.


I
Fuming HNO3 cold
II
Fuming HNO3 hot
III
Sn,HCl
NaNO2, HCl
KI
Na/Hg
diazotization
IV
KMnO4 KOH
V
P/HI
VI
dilute HNO3 hot
VII
KOH 290-300°
VIII
+ (CH3)2CO

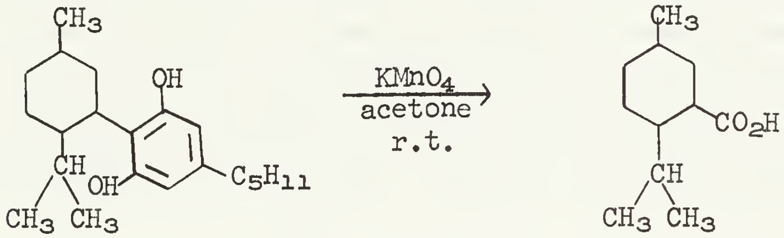


IX

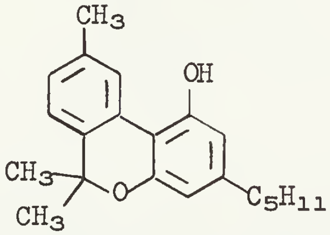
Cannabidiol, another material found by Adams and Todd in the high boiling fraction of marihuana was seen immediately to possess a molecular formula $C_{21}H_{30}O_2$ quite similar to cannabinol.[7] It had two acidic hydroxyl groups which were readily acetylated. Ultraviolet spectral comparison showed the phenolic hydroxyls to be in a resorcinol arrangement. Under mild hydrogenation conditions it rapidly consumed two moles of hydrogen without great change in the UV chromophore, indicating that the phenolic ring remained unchanged.[8] Treatment of cannabidiol with pyridine hydrochloride yielded conclusive proof of its general structure when p-cymene and olivetol were formed.[9]



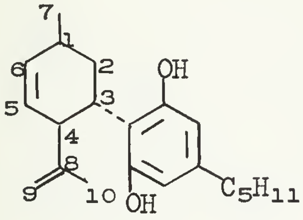
The point of attachment of the two rings was determined by oxidizing tetrahydrocannabidiol. The resulting menthane carboxylic acid was isolated as its anilide.[9]



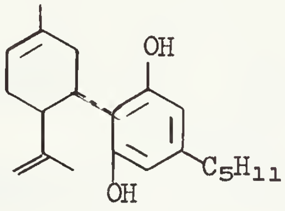
Assuming cannabinol to be similar to cannabidiol, the last data suggested the correct structure for cannabinol. Synthesis of this structure confirmed the identity of cannabinol.[10,11]



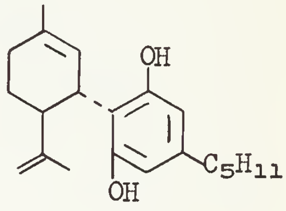
Recently, using modern analytical techniques Mechoulam and Shvo[12] have completed the structural elucidation of cannabidiol. Earlier work by Adams et al.[13] on placement of the two non-aromatic double bonds had demonstrated that a terminal double bond was present by recovering formaldehyde on ozonization of cannabidiol. Ultraviolet studies of model compounds further showed that the second double bond was neither conjugated with the aromatic ring nor with the terminal isopropylene double bond.[13] Consequently, the remaining double bond could be located only in positions Δ^5, Δ^6, or Δ^1. On NMR analysis, Mechoulam and Shvo observed 3 olefinic protons and



Δ^5



Δ^6

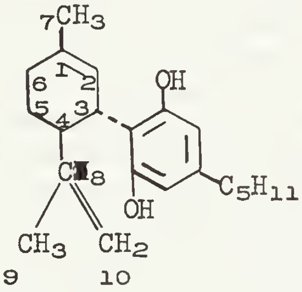


Δ^1

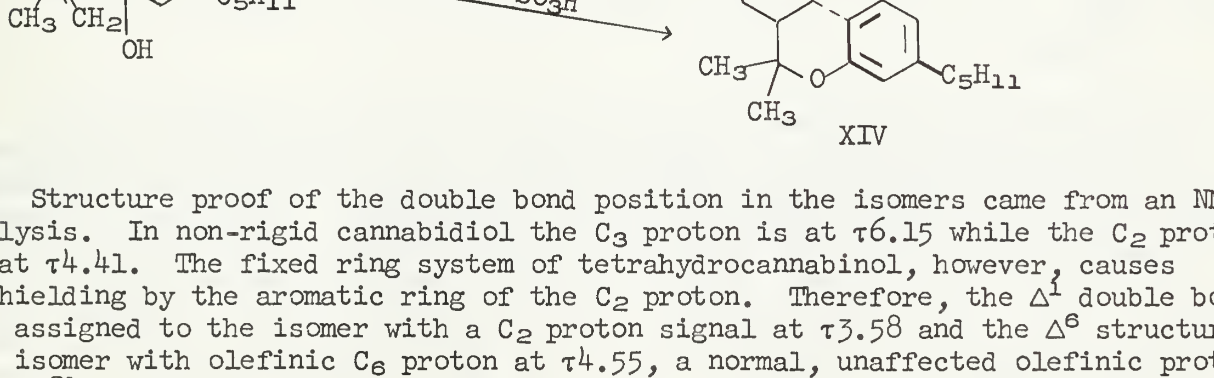
2 olefinic methyl groups in the spectrum of cannabidiol. These data eliminated the Δ^5 isomer as a possibility. The NMR spectrum further showed the C_3 proton at τ6.15. Normally a benzyl proton appears around τ7.13.[14] This datum indicated the proximity of another deshielding force, the double bond. The C_3 proton appeared as a doublet (J = 11) which is not appreciably coupled with the C_2 proton. If cannabidiol has the double bond in the Δ^1 position, then C_2 would be at an angle of approximately 85^0 and consequently not appreciably coupled to C_3. On hydrogenation the product, tetrahydrocannabidiol, shows the C_3 proton at τ7.40. If the Δ^6 isomer were the correct structure, little change in the C_3 proton position would be expected. A final experiment was a selective epoxidation on the ring double bond of cannabidiol

bisdinitrobenzoate with perbenzoic acid. The NMR spectrum of the product showed no change in the position of the methyl group or protons surrounding the side chain double bond but the C_1, C_2 and C_3 groups did change. In particular the C_3 proton was now observed as a doublet at $\tau 6.70$, again indicating the proximity of the epoxide linkage. From the data it was concluded that cannabidiol is the Δ^1 isomer.[12]

Evidence leading to the stereochemistry at carbon 3 and 4, the final structural unknown, initially came when Adams oxidized tetrahydrocannabidiol with potassium permanganate in acetone and obtained menthane carboxylic acid as one of the products.[9] He also found that L-menthyl chloride could be converted via Grignard formation and carbonation to the same menthane carboxylic acid. Later work by Roberts, Shoppee and Stephenson[15] has shown that both 3α and 3β-bromocholestane are converted to cholestane-3β-carboxylic acid. Assuming a similar reaction with menthyl chloride, an equatorial carboxyl group would be expected thus giving the thermodynamically most stable eee isomer. In other evidence, the coupling constant $J = 11$ for the C_3 proton coupling with C_4 proton is indicative of a diaxial conformation and thus a trans ring junction.[12] These data then indicate that cannabidiol has a 3,4-trans ring junction. The total structure is seen below.



Early investigations by Adams et al. had shown that naturally occurring cannabidiol could be converted with acids to two optically active, psychotomimetically active products.[16] Sulfur dehydrogenation converted these materials to cannabinol thus proving their structures as tetrahydrocannabinols.[17] Furthermore, both of the isomers when hydrogenated yielded the same two epimers, proven similar by IR, NMR and chromoplate comparison.[18] Recent investigations have shown that treatment of cannabidiol with a catalytic amount of p-toluenesulfonic acid produces the Δ^6-3,4-trans-tetrahydrocannabinol, XIV, while treatment of cannabidiol with dilute hydrochloric acid in ethanol produces XV, the Δ^1-3,4-trans-tetrahydrocannabinol.[18-21]



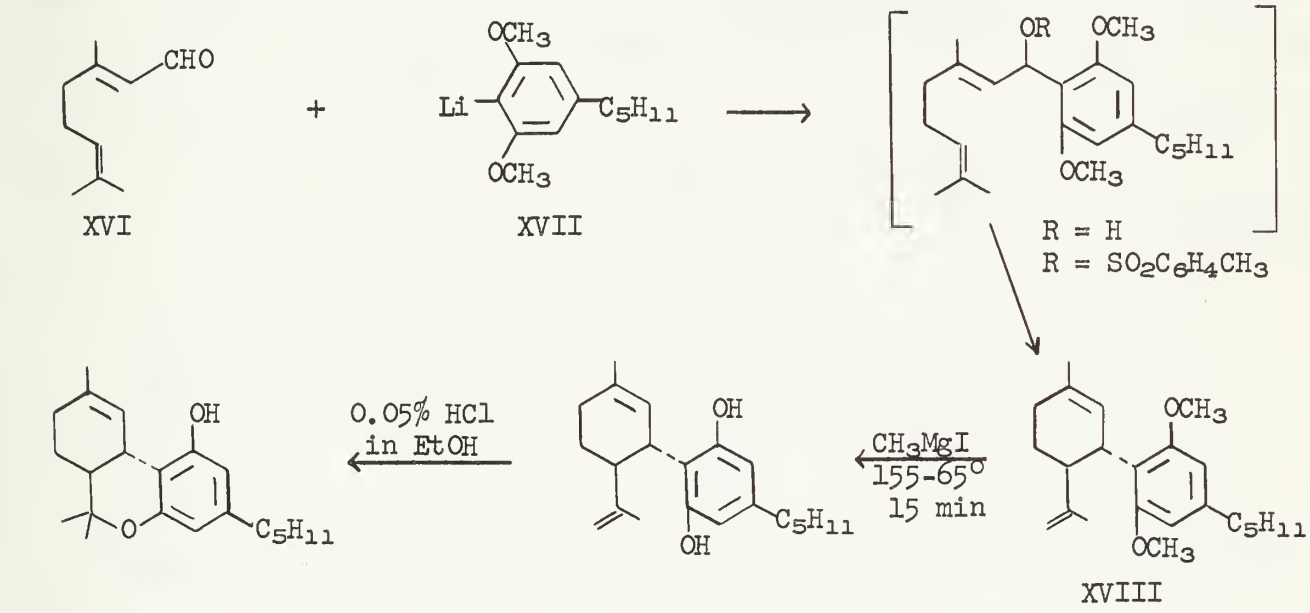
Structure proof of the double bond position in the isomers came from an NMR analysis. In non-rigid cannabidiol the C_3 proton is at $\tau 6.15$ while the C_2 proton is at $\tau 4.41$. The fixed ring system of tetrahydrocannabinol, however, causes deshielding by the aromatic ring of the C_2 proton. Therefore, the Δ^1 double bond was assigned to the isomer with a C_2 proton signal at $\tau 3.58$ and the Δ^6 structure to the isomer with olefinic C_6 proton at $\tau 4.55$, a normal, unaffected olefinic proton value.[21]

Both the Δ^1 and Δ^6 isomers are psychotomimetically active. Taylor et al.[22] have found the Δ^1 isomer to isomerize partially to the Δ^6 isomer when chromatographed at 280° (column 10% GE-SE-30 on Diatoport S). From this observation, they suggest that on smoking marihuana, the psychotomimetic effect may be due to the Δ^6 isomer instead of the Δ^1. Gaoni and Mechoulam[20] disagree after finding no isomerization of the Δ^1 isomer to the Δ^6 isomer in gas chromatographic experiments up to 300° using a different column (SE-30 on Chromosorb W). Recent experiments by Lerner and Zeffert[3] have shown by using a smoking machine and analyzing the smoke by GC that the Δ^6 isomer increased from 3% to only 9% of the total Δ^1, Δ^6-tetrahydrocannabinol content. This would suggest that although some isomerization does occur on smoking, the major psychotomimetically active component is still the Δ^1 isomer.

By treatment with p-toluenesulfonic acid in toluene, the Δ^1 isomer can be converted 90% to the Δ^6 isomer.[19] These same workers have also noted a slow isomerization of the Δ^1 to Δ^6 isomer on long standing.[19] Gaoni and Mechoulam[20] suggest the facile isomerization occurs because there is much less steric crowding in the Δ^6 isomer between the phenolic hydroxyl and the C_2 protons.

TOTAL SYNTHESIS OF TETRAHYDROCANNABINOLS

Mechoulam and Gaoni recently reported the first total synthesis of a psychotomimetically active constituent of marihuana, dl-Δ^1-3,4-trans-tetrahydrocannabinol.[23] Initially citral a XVI was condensed with the lithium derivative of olivetol dimethyl ether XVII. This condensation led to a complicated mixture which was dissolved in pyridine and treated with p-toluenesulfonyl chloride to form the sulfonate ester followed by ring closure and sulfonate elimination. Chromatography of the mixture over 10% silver nitrate and alumina yielded a fraction with polarity similar to natural cannabidiol dimethyl ether. Rechromatography of this material yielded dl-cannabidiol dimethyl ether XVIII in low yield. Demethylation with methylmagnesium iodide gave an 80% yield of dl-cannabidiol which upon treatment with 0.05% hydrochloric acid gave dl-Δ^1-3,4-trans-tetrahydrocannabinol.



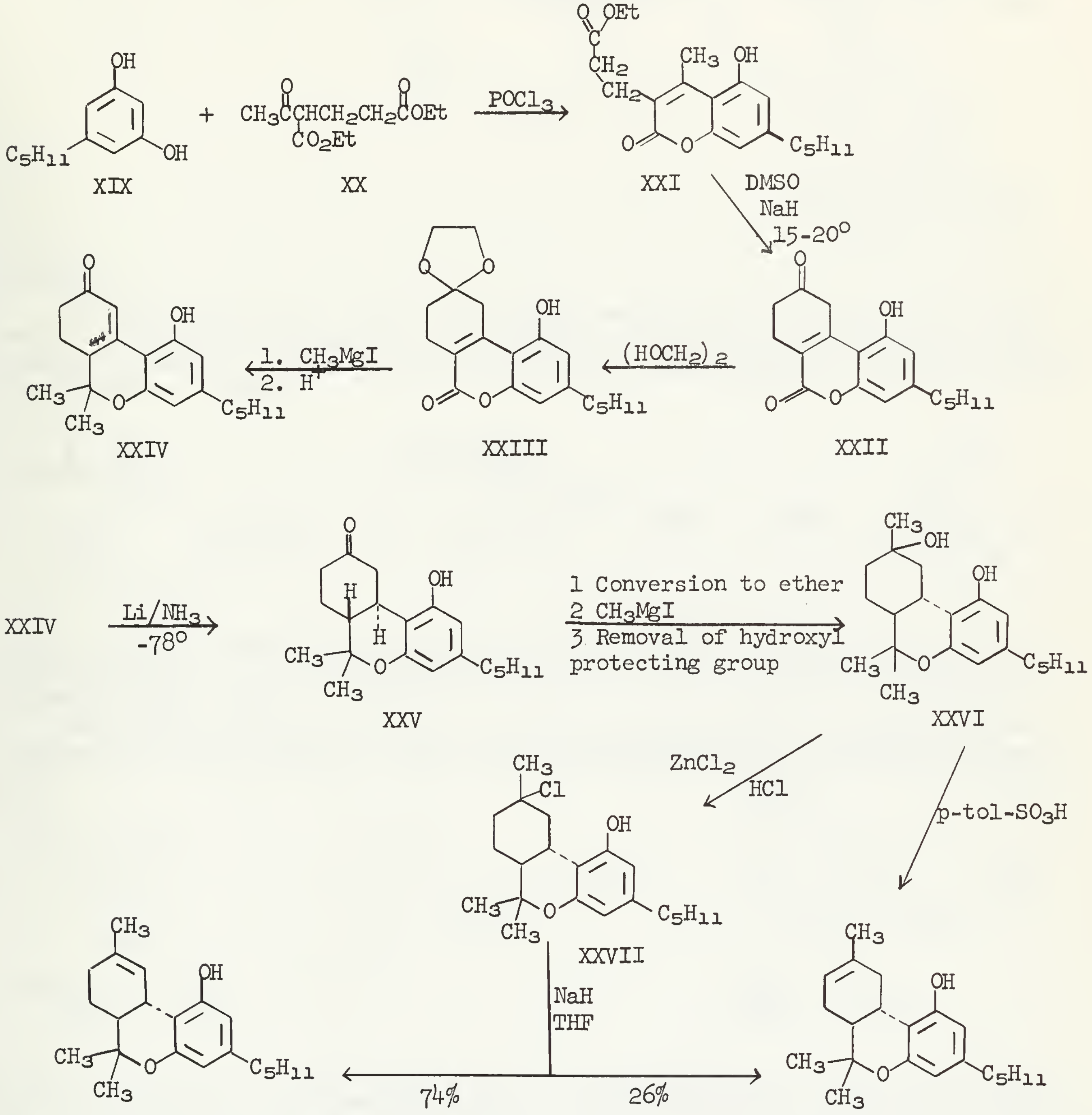
XVI

XVII

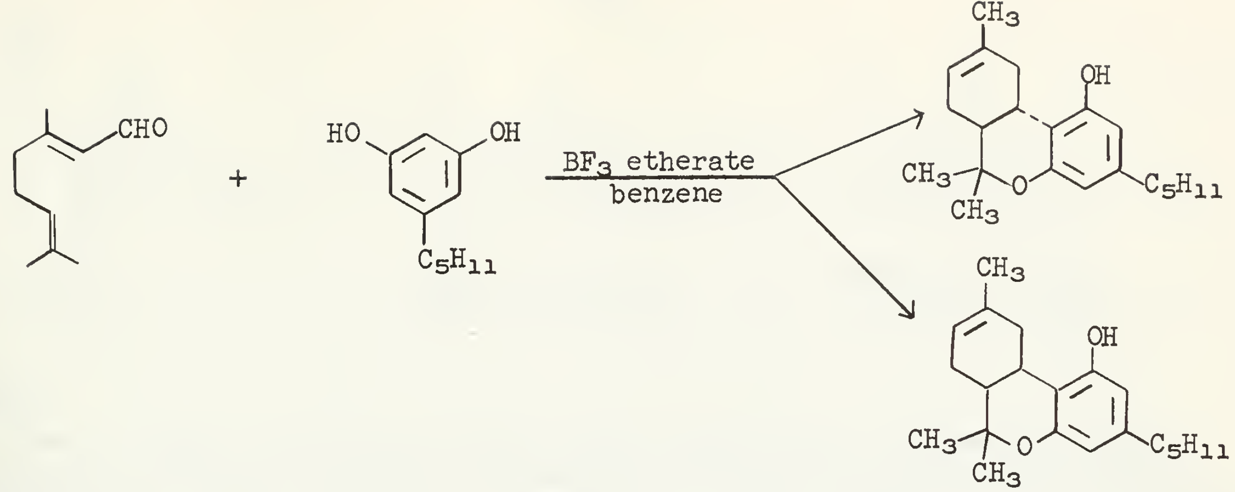
XVIII

A second synthesis of both dl-Δ^1 and Δ^6-3,4-trans-tetrahydrocannabinol was carried out by Fahrenholtz, Lurie and Kierstead.[24] This synthesis involved a Pechmann condensation of olivetol XIX with diethyl-α-acetoglutarate XX to form the expected coumarin XXI. Cyclization of XXI using sodium hydride in an aldol type condensation gave XXII. Ethylene glycol converted XXII into the corresponding ketal XXIII which exists in two polymorphic forms. Reaction of the ketal with methyl magnesium iodide followed by acidic hydrolysis gave XXIV. Birch reduction converted XXIV to the trans ketone XXV. Carbinol XXVI was obtained by conversion of XXV to its tetrahydropyranyl ether followed by treatment with methyl magnesium iodide and subsequent cleavage of the protecting group. Dehydration of XXVI using

a catalytic amount of p-toluenesulfonic acid in benzene gave dl-Δ^6-3,4-trans-tetrahydrocannabinol as a single isomer shown by glpc. Treatment of XXVI with Lucas reagent gave the corresponding chloride XXVII. Dehydrohalogenation of XXVII with sodium hydride in refluxing tetrahydrofuran gave in quantitative yield a mixture of the Δ^1, 74%, and the Δ^6, 26%, tetrahydrocannabinol isomers as shown by glpc.

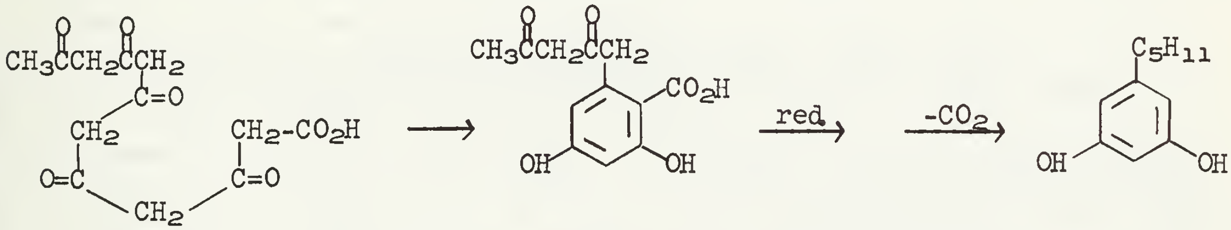

XIX
XX
POCl₃
XXI
DMSO
NaH
15-20°
XXII
(HOCH₂)₂
XXIII
1. CH₃MgI
2. H⁺
XXIV
XXIV
Li/NH₃
-78°
XXV
1 Conversion to ether
2 CH₃MgI
3 Removal of hydroxyl protecting group
XXVI
ZnCl₂
HCl
p-tol-SO₃H
XXVII
NaH
THF
74%
26%

Recently Taylor, Lenard and Shvo carried out a one step synthesis utilizing citral and olivetol in the presence of a 10% benzene solution of boron trifluoride etherate.[22] Chromatography of the mixture over Florisil followed by preparative VPC separation gave a 20% yield of dl-Δ^6-3,4-trans-tetrahydrocannabinol. Some of the Δ^6-cis isomer was also obtained and identified by comparison with a sample of the cis isomer prepared by an independent, unequivocal route.


CHO
HO
OH
C_5H_{11}
+
BF_3 etherate
benzene
CH_3
OH
CH_3
CH_3
O
C_5H_{11}

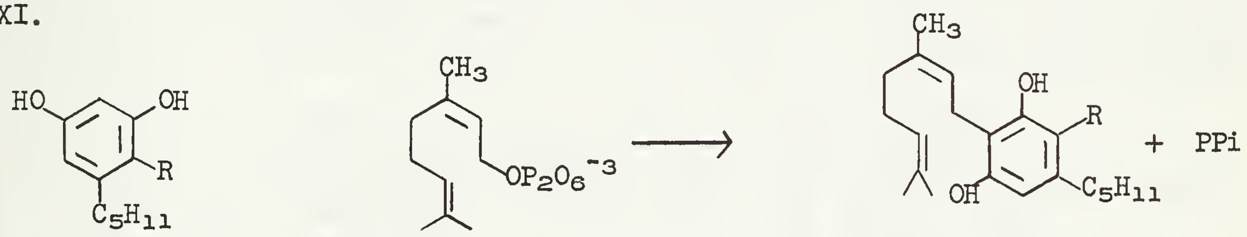
BIOGENESIS

No labelling studies have been performed as yet, but by examination of the other constituents of marihuana, the following biogenetic pathway has been postulated. Olivetol probably is formed via the usual head to tail linking of acetate units to form phenolic compounds.


$CH_3\overset{O}{C}CH_2\overset{O}{C}CH_2$
C=O
CH_2
$CH_2\text{-}CO_2H$
O=C
C=O
CH_2
CO_2H
OH
red.
$-CO_2$
C_5H_{11}

It is uncertain whether the pentyl side chain is formed from acetate units or whether hexanoic acid is incorporated directly.[25] Also in question is when the decarboxylation occurs.

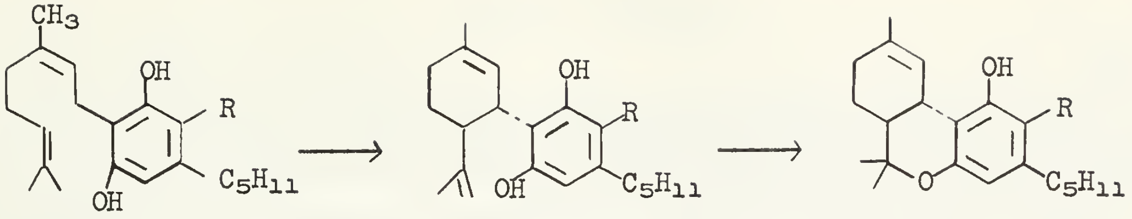
Once formed, olivetol XXVIII or the acid precursor XXIX probably condenses with geranyl pyrophosphate to form either cannabigerol XXX or cannabigerolic acid XXXI.


HO
OH
R
C_5H_{11}
CH_3
$OP_2O_6^{-3}$
CH_3
OH
R
OH
C_5H_{11}
+ PPi

XXVIII R = H
XXIX R = CO_2H

XXX R = H
XXXI R = CO_2H

Both cannabigerol and cannabigerolic acid have been found in extracts of marihuana.[21] These two materials then condense further to the corresponding cannabidiol XXXII and tetrahydrocannabinol XXXIII or cannabidiolic acid XXXIV and tetrahydrocannabinolic acid XXXV.[26,27] Whether the carboxylate derivatives are converted in part in any of the preceeding steps to the decarboxylated derivatives is still uncertain. The carboxylated derivatives have a high antibiotic activity against gram positive bacteria which marihuana lacks and they may only compose another metabolic pathway of the plant.[26]



R = H
R = CO_2H

XXXII R = H
XXXIV R = CO_2H

XXXIII R = H
XXXV R = CO_2H

SUMMARY

Recent studies have fully elucidated the structures of the natural psychotomimetically active constituents of marihuana, Δ^1 and Δ^6-3,4-trans-tetrahydrocannabinol and a likely precursor, cannabidiol. Total synthesis of the dl forms has also been accomplished. Speculations on the biogenetic pathway have been advanced.

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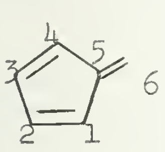
BENZENE PHOTOLYSIS

Reported by Warren J. Peascoe March 9, 1967

Many examples of reactions involving electronically excited benzene have recently been reported. This seminar will review these reactions. A brief summary of the general processes which occur upon absorption of a quantum of energy is presented.

Absorption of a quantum of energy by a molecule in the ground state S_0 produces an excited singlet which may return to the ground state by various photophysical processes.[1] Singlets in the higher excited states S_2, S_3, . . . undergo internal conversion to the first excited singlet state S_1 or undergo intersystem crossing to produce triplets. The S_1 singlet may also undergo intersystem crossing to produce a triplet, or it may return to the ground state by internal conversion or fluorescence. The higher excited triplets rapidly undergo internal conversion to the T_1 state and may return to the ground state by intersystem crossing or by phosphorescence.

The irradiation of benzene vapor with light in the 2300-2700 A region has recently been reviewed by Noyes,[2,53] who concluded that the absorbed energy is efficiently dissipated by photophysical processes. Irradiation at a shorter wavelength, 1849 A, has been reported by several groups to lead to the formation of polymer deposited on the walls of the reactor, two transient intermediates, and minor amounts of hydrogen, methane, acetylene, ethane, toluene, and a C_2 or C_3 substituted benzene.[3-8,55] The quantum yield (number of molecules which undergo a specific reaction/number of molecules electronically excited) of the formation of hydrogen was reported to be about 0.02 by Lipsky and coworkers,[3] and Foote and coworkers reported the formation of acetylene with a quantum yield of 0.015.[4] The major transient intermediate has been identified as fulvene 1 independently by Ward and coworkers[5] and by Kaplan and Wilzbach[55].



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It was purified by preparative gas chromatography and had the same uv, ir, nmr, and mass spectra as authentic fulvene. Fulvene was shown to be the same intermediate detected but not identified by the Foote[4] and Lipsky[6] groups by a comparison of the vapor phase ultraviolet spectra and retention time on gas chromatography. The minor intermediate in approximately 1/6 the concentration of fulvene was detected by Kaplan and Wilzbach by gas chromatography and by its uv spectrum.[55] Since it absorbed in the same region as fulvene, its uv spectrum was determined from the difference between the uv spectrum of irradiated benzene, vs. benzene blank, and the spectrum of fulvene vapor in the same concentration as in irradiated benzene. On the basis of its uv absorption ($\lambda_{max}^{cyclohexane}$ 2500 A) and extinction coefficient (log $\epsilon \sim 4.5$), 1,3-hexadiene-5-yne was proposed as a possible structure.

The Foote and Lipsky groups both observed that fulvene formed rapidly and reached a low steady-state concentration. The initial rate of formation of fulvene was found to be inversely proportional to the pressure of added nitrogen by Foote and coworkers for nitrogen pressures of less than one atm;[4] Lipsky and coworkers found that the rate of formation decreased with increasing nitrogen pressure from 0.1 to 50 atm.[6] The quantum yield for the disappearance of benzene was also inversely related to the pressure; it was 1 at benzene pressures of less than 0.1mm[4], fell to 0.25 at 1mm, and decreased further if nitrogen was added.[6] This dependence on pressure indicated that the reaction was collision quenched. The polymer seemed to be formed by a further reaction of fulvene since the ratio of the quantum yield of benzene disappearance to the quantum yield of the formation of fulvene was a constant as the nitrogen pressure was varied.

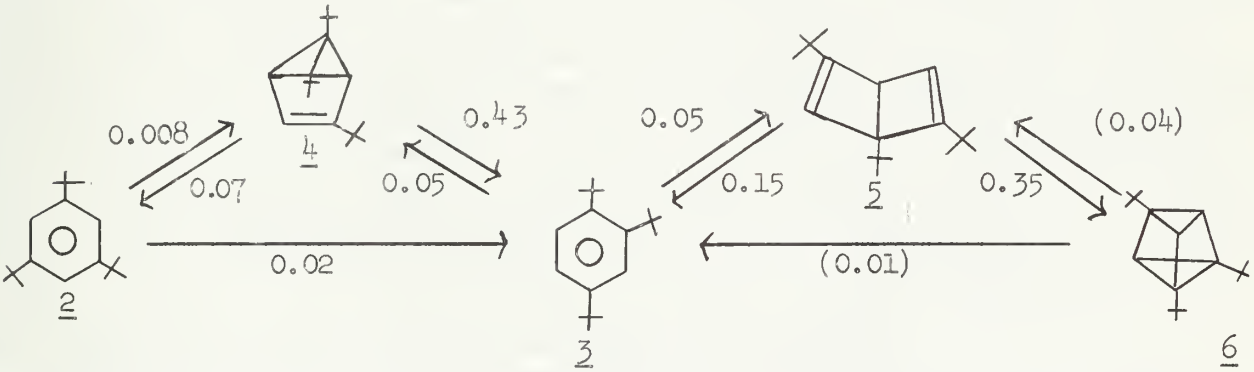
Lipsky and coworkers calculated from the absorption oscillator strengths that the second and third excited benzene singlets had fluorescence lifetimes of less than 10^{-12} sec.[9] Since no fluorescence was observed from these states, the state lifetime must be even shorter; and a pressure of ca. 100 atm is required

in order to have the mean time between collisions equal the calculated fluorescence lifetime. Fluorescence and triplet sensitized emission of biacetyl were observed upon excitation of benzene to the S_1 state with light of wavelength greater than 2200 A. However, neither fluorescence from any singlet state nor sensitized emission of biacetyl was observed upon excitation with light of wavelength in the 2200-1600 A region corresponding to excitation to the S_2 or S_3 state. Thus either a direct photochemical reaction or very efficient internal conversion to the ground state is required from the S_2 and S_3 states. The observed collision quenching at low pressures ruled out a direct photoreaction upon irradiation at 1849 A. Lipsky and coworkers were led to propose that the initially excited S_3 or S_2 benzene very rapidly underwent internal conversion to vibrationally excited ground state which either lost its vibrational energy to produce benzene or isomerized to fulvene.[6]

The irreversible formation of fulvene and polymer upon irradiation of liquid benzene at wavelengths greater than 2000 A under nitrogen atmosphere was reported by Bryce-Smith and coworkers,[10,11] with an approximate quantum yield of 0.01. The uv spectrum of the product resembled that of authentic fulvene, and the one-to-one adduct formed between it and maleic anhydride was found to have the same infrared spectrum and mixed melting point as the adduct prepared from authentic fulvene.

The photolytic isomerization of orthodisubstituted benzenes has been reviewed through 1964 in a previous seminar.[12] The isolation of substituted dewar benzenes and isomerizations through interconvertible dewar benzenes were discussed. Additional examples of isomerizations of substituted benzenes have been reported. The formation of perfluorodewar benzene from the irradiation at 2537 A of perfluorobenzene in the vapor phase has been independently reported by Haller[13] and by Camaggi and coworkers.[14] Lemal and Lokensgard[15] have converted hexamethyldewar benzene into a mixture of 20% hexamethylprismane and hexamethylbenzene upon irradiation at 2537 A in butane solution. The hexamethylprismane could be photochemically converted to the dewar benzene and hexamethylbenzene.

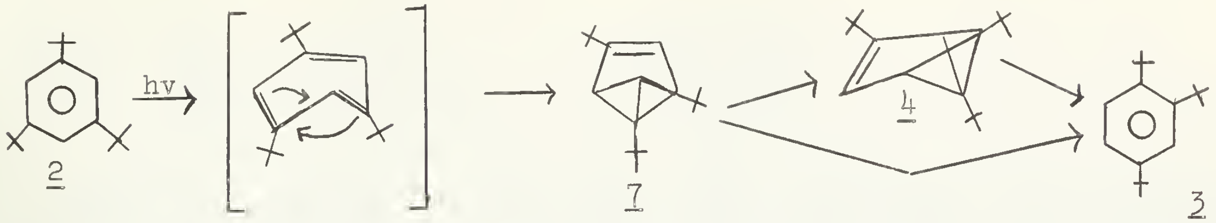
Wilzbach and Kaplan have reported that 1,3,5-tri-*t*-butylbenzene 2 photoisomerized at 2537 A in isohexane to 1,2,4-tri-*t*-butylbenzene 3 through a benzvalene intermediate 4.[16] Irradiation of 2 or 3 led to a photostationary mixture with 7.3% 2, 20.6% 3, less than 0.7% 4, 7.1% 5, and 64.8% 6. Two fulvenes were also produced in low yield from 2. The product mixtures were analyzed by nmr

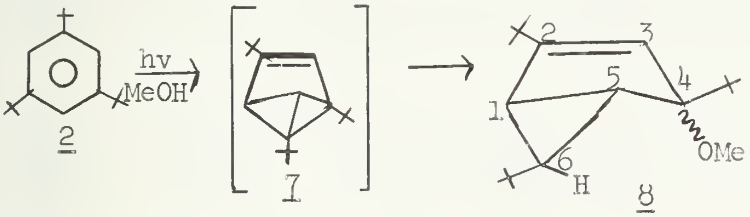


utilizing the characteristic *t*-butyl peaks, and the quantum yields shown in the diagram were determined for separate isomers 2, 3, 4, and 5. The prismane 6 could not be completely separated from the dewar benzene 5 and the quantum yields for its reactions are approximate. The products were identified on the basis of their spectral properties and rearomatization reactions on heating. The benzvalene 4 showed a nmr methyne proton ABX pattern, τ 8.27, 8.35, and 4.95 for A, B, and X respectively, with J_{AB}=6.65, J_{AX}=2.45, and J_{BX}=1.25 cps. The *t*-butyl protons were observed at τ 8.94 (18 H) and 8.99 (9 H). The benzvalene rearomatized upon heating exclusively to 3 leading to the assignment of structure 4.

The simplest method for photoconversion of 3 into 4 involves bending the

planar ring of 3 along with the formation of transannular bonds; a similar ring bending of 2 along with the formation of transannular bonds leads to 7 rather than 4. Wilzbach and Kaplan did not report the isolation and identification of the intermediate initially formed from the irradiation of 2, and thus 7 rather than 4 may be the intermediate in the photoisomerization of 2 into 3. It is possible that 7 may not have been detected since the nmr chemical shifts of the *t*-butyl protons of 7 would be expected to be very similar to the chemical shifts of the *t*-butyl protons of 4. A second possibility is that 4 was the intermediate and that it was formed from the isomerization of 7 in the ground or excited state. As a member of the class of valene compounds, the isomerization of benzvalene 7 to benzvalene 4 might be expected.[17] Evidence that irradiation of 2 leads to the initial formation of 7 in either an excited state or in the ground state has been reported by Kaplan and coworkers.[18] They found that 2 irradiated in methanol produced 8 with a quantum yield of 0.15 and that no isomeric tri-*t*-butylbenzenes were formed. The product was identified by its spectral properties, and the proton in position 6 was assigned the *endo*-configuration on the basis of its nmr chemical shift, τ 9.27, and coupling constants $J_{1,6}$=4.6 and $J_{5,6}$=2.7 cps. The *t*-butyl groups were shown not to be on adjacent carbons by thermal conversion of 8 into 1,3,6-tri-*t*-butylfulvene.

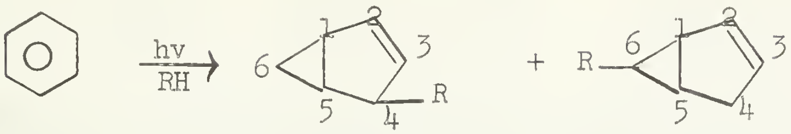




The formation of benzvalene upon irradiation of benzene in the liquid phase at 2537 A has been reported by Kaplan and coworkers[56]. Concentrations of product (1% based on benzene) high enough for nmr spectroscopy and preparative gas chromatography were obtained by irradation of dilute solutions of benzene in hexadecane at 65°. Treatment with methanolic HCl of either irradiated benzene or the product purified by preparative gas chromatography and absorbed in isohexane produced two products identified by methods not described as 6-*endo*-methoxy (3.1.0)bicyclo-2-ene, 10 ($R=OCH_3$), and one of the 4-methoxy isomers, 9 ($R=OCH_3$). The uv spectrum of the irradiated benzene product showed no maximum above 2100 A but had a broad shoulder between 2200 A and 2300 A ($\epsilon \sim 2500$). The nmr spectrum of the product showed three resonances of equal area: an unsymmetrical triplet (1.5-and 1.7-cps couplings) at τ 4.04, a symmetrical triplet (1.5-cps couplings) at τ 6.47, and a quintet (Σ J=6.2 cps) at τ 8.16. The product rearomatized only slowly at room temperature and was assigned the benzvalene structure.

Photoaddition reactions have been reported which may be rationalized as formal additions to benzvalene and to dewar benzene. Farenhorst and Bickel[19] reported that benzene irradiated in acetic acid with a low pressure mercury lamp produced polymer, 9 ($R=-OCOCH_3$), and two other unidentified products in lesser amounts. The acetoxy group of 9 ($R=-OCOCH_3$) is reportedly in the *exo*-position from nmr analysis, but only chemical shifts without any splitting patterns were reported. Without nmr data for the *endo*- and *exo*-compounds the stereochemistry must remain tentative. Compound 9 ($R=-OCOCH_3$) could not be hydrolyzed in either mild acid or base but in both cases produced polymer and a yellow discoloration due to fulvene as indicated by the uv spectrum. Irradiation of aqueous phosphoric acid saturated with benzene produced two products tentatively identified as aldehydes by their spectra and an alcohol 9 (R= OH) with the hydroxy group in the

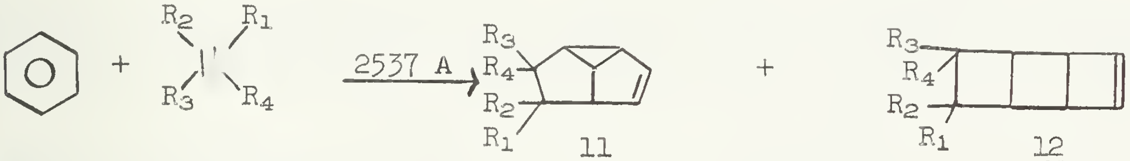
exo-position. The stereochemistry of the hydroxy group was based only on reported nmr chemical shifts.



9 10

Kaplan and coworkers[18] reported that benzene irradiated in trifluoroethanol yielded 9 and 10 ($R{=}OCH_2CF_3$) in the ratio of 2:1 with a total quantum yield of 0.05. The identification of the products was based on spectral data. Nmr double resonance analysis of 10 ($R{=}OCH_2CF_3$) showed H_6 to be coupled with H_1 and H_5 (J=7cps) indicating an *exo*-position for H_6 to the authors. The coupling constant is closer to the reported vicinal cyclopropyl coupling constants 5.2 to 8.0 cps for *trans* hydrogens than to 8.0 to 11.2 cps for *cis* hydrogens,[57] and the opposite stereochemistry, H_6-*endo*, is indicated at C_6. The stereochemistry of 9 ($R{=}OCH_2CF_3$) was not determined.

The photolytic formal addition of olefins to benzvalene has also been reported by two groups. Wilzbach and Kaplan[20] reported that products corresponding to 11 could be isolated by gas chromatography from the product mixtures from the irradiation at 2537 A of benzene and ethylene, *cis*-2-butene, cyclopentene, or 2,3-dimethylbut-2-ene. The products were characterized by their spectral properties and extensive nmr decoupling experiments. Bryce-Smith and coworkers[21] reported that equimolar mixtures of cyclooctene and benzene at room temperature



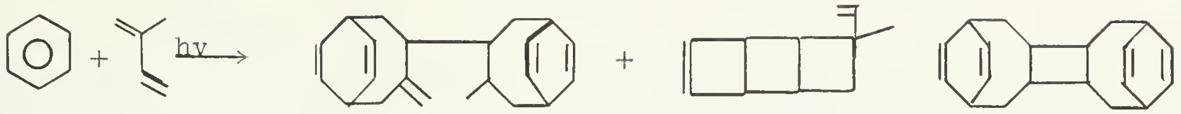
11 12

or at -60° irradiated in the 2350-2580 A region produced two 1:1 addition products in the ratio of 8:1. Benzophenone and acetone were ineffective as sensitizers but β-propiolactone increased the rate of addition two-fold. The major product 11 was characterized by spectral studies, products from catalytic hydrogenation, and formation of 1:1 adducts with tetracyanoethylene or phenyl azide. But-1-ene, oct-1-ene, cyclohexene, cycloocta-1,5-diene, and ethyl vinyl ether also gave 1:1 photoadducts analogous to 11. The structure of the minor product was suggested to be 12 on the basis of a sharp olefinic singlet at τ 4.43. Srinivasan and Hill[22] reported the formation of 12 in 50% yield from the photoaddition of benzene and cyclobutene at 2537 A. The product was identified on the basis of its spectra (a sharp nmr resonance for two olefinic protons at τ 4.25) and the products produced upon catalytic hydrogenation. Upon heating to 200°, the product decomposed to produce benzene and butadiene.

Bryce-Smith and coworkers[23] have noted that both 11 and 12 provide an olefinic functional group and should be able to add a second molecule of benzene in a step towards photopolymerization. They irradiated benzene and small amounts of cyclooctene (0.35 mole-%) or the cyclooctene-benzene 1:1 adduct (0.06 mole-%) for 100 hr with a medium pressure mercury lamp and found a polymer to be produced. The polymer was fractionated by its solubility in hexane, acetone, benzene, and chloroform. The major fraction in benzene had a molecular weight of about 1500. There were no aromatic protons in the nmr spectrum, and the ir spectrum showed six of the seven bands observed in monomeric 11. The trace amount of olefin was sufficient to suppress effectively the formation of fulvene. Polymers with different properties were reported to be formed with light of wavelength of ca. 2000 A.

Koltzenburg and Kraft[24,25] reported the photoaddition of 1,3-dienes to benzene upon irradiation at 2537 A. Gas chromatography showed at least ten products from the reaction of isoprene with benzene with a 46% yield of 13 and a 23% yield of 14.

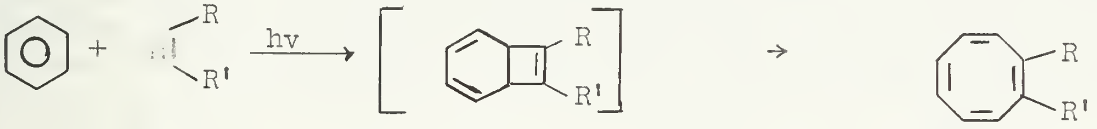
The products 13 and 14 were identified on the basis of their chemical and spectral properties. Toluene, o-xylene, perfluorobenzene, and 1,2,4,5-tetrafluorobenzene have also been found to form dimeric adducts with isoprene. The photoadduct from butadiene and benzene dimerized to form 15. Attempts to sensitize the reaction with benzophenone led only to the formation of dimeric dienes.



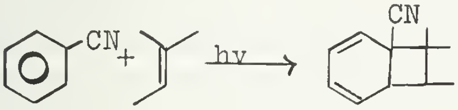
13 14 15

A 2:1 photoadduct formed from maleic anhydride or N-substituted maleimide and benzene has been reported.[26-29] These reactions which proceed by photoactivation of the substrate or a charge-transfer complex between substrate and benzene, rather than by direct photoactivation of benzene, will not be discussed.

Two more photoaddition reactions for which no evidence is available for determination of the excited reacting species must be considered. The photoaddition of methyl acetylenecarboxylate or dimethyl acetylenedicarboxylate to benzene has been reported by two groups to produce substituted cyclooctatetraenes 17.[30-32] The reaction is thought to proceed by 1,2-addition to benzene to form 16 which isomerizes to 17. The cyclooctatetraene acid formed by saponification of the ester was identical with the acid prepared by an alternate route. The diacid was assigned structure 17 on the basis of its spectra and products produced by catalytic hydrogenation. The formation of 18 by photoaddition of 2-methylbut-2-ene to benzonitrile has been reported by Atkinson and coworkers.[33] They found that benzophenone effectively quenched the reaction and that aliphatic acetylenes added to give cyclooctatetraenes 19.



16 17



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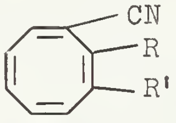
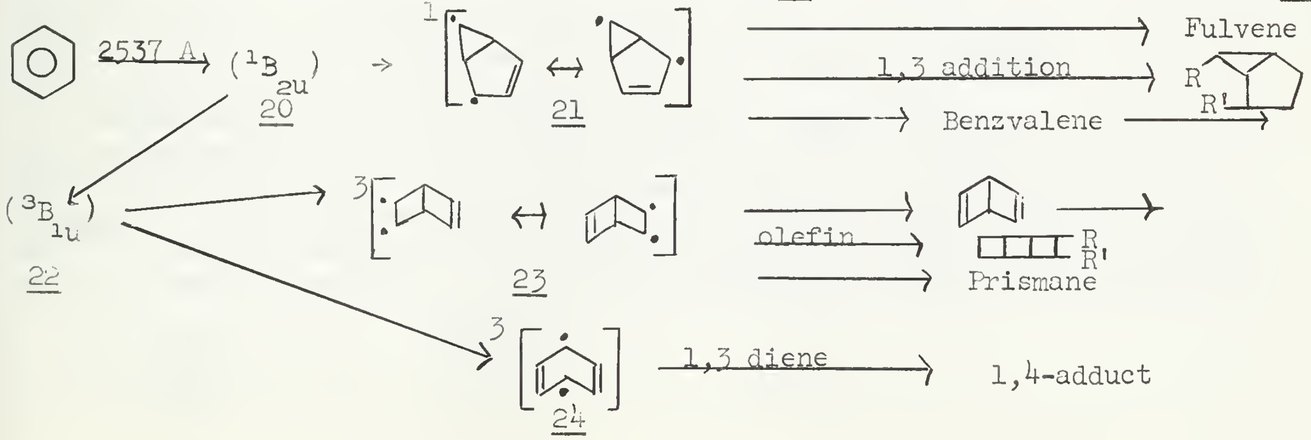


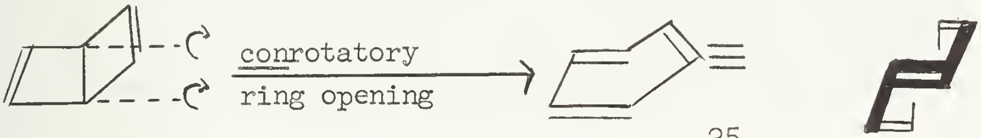
19

To account for the photoisomerizations and photoaddition reactions, Bryce-Smith and Longuet-Higgins have proposed a mechanism which allows the rationalization of the observed products in terms of the lowest benzene singlet and triplet.[34] The first benzene singlet which has B_{2u} symmetry[35] is antisymmetric about a plane through any opposite pair of carbon atoms; the lowest electronic configuration of the singlet biradical 21 is also antisymmetric about its plane of symmetry. An orbital correlation diagram[36] indicates that 20 may pass adiabatically into 21.



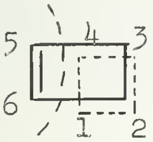
Similarly one component of the lowest benzene triplet, which has B_{1u} symmetry[37] and is antisymmetric about a plane bisecting any opposite pair of carbon-carbon bonds, may adiabatically pass into the triplet state of either of the diradicals 23 or 24. The lowest electronic configuration of both 23 and 24 in the triplet state is antisymmetric about a plane bisecting the terminal bonds of 23 and the double bonds of 24. The diradicals are proposed to react as indicated to form the observed products from electronically excited benzene. There is no experimental evidence which requires the diradicals 21, 23, and 24 to be on the reaction path leading from electronically excited benzene to products, and it is possible that benzene in the lowest singlet or triplet state reacts directly to form the observed products. The experimental determination of the multiplicity of the electronically excited state leading to the formation of dewar benzene, dewar benzene addition products, prismane, and 1,4-addition products would be useful in evaluating this mechanism since triplet states are predicted. The formation of cyclooctatetraenes by the 1,2-addition of acetylenes to benzene and the 1,2-addition to benzonitrile were not explicitly considered by the authors. It has not been established that these reactions must proceed by attack of excited benzene on the substrate. An alternate mechanism, attack of excited substrate on benzene, would not require modification of the proposed reaction scheme.

An alternate mechanism involving a single highly reactive intermediate has been proposed by Farenhorst.[38] van Tamelen[39] has pointed out that the Woodward-Hoffmann rules[40] predict preferential *conrotatory* ring opening of cyclobutene systems, and that *conrotatory* ring opening of dewar benzene leads to *trans*-benzene 25.



25

The *trans*-benzene *pi*-orbitals are topologically equivalent to a conjugated six-membered Moebius ring. The HMO energy calculated by Heilbronner[41] for a ground state six-membered Moebius system was shown to be equal to the HMO energy of benzene in its first excited state. Farenhorst thus proposed that benzene in an excited state isomerized to *trans*-benzene in the ground electronic state with a Moebius *pi*-electronic structure and that the *trans*-benzene reacted to form the observed products. He also pointed out that a possible transition state 26 leading to the formation of dewar benzene and a transition state 27 leading to benzvalene would have nearly the same energy as *trans*-benzene. These transition



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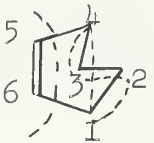
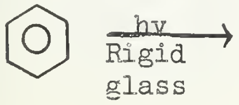


27

states consist of a localized double bond (C_5-C_6) and a conjugated four-membered Moebius ring (C_1,C_2,C_3,C_4); the transition state 27 also contains transannular bonds between C_1 and C_3 and between C_2 and C_4.

Irradiation at 2537 A of benzene in rigid organic glasses at liquid nitrogen temperature has been studied by many groups.[42-54] A product proposed by Anderton and coworkers to be a substituted hexatriene was detected by its uv spectrum.[43] The position of the three observed peaks varied with the solvent used to form the rigid glass.[43-46] Migirdicyan and coworkers reported that the product from the reaction in ethanol 28 (R= CHOHCH$_3$) dehydrated on preparative



$H(CH=CH)_3R$ $H(CH=CH)_3R$

28

gas chromatography to produce 1,3,5,7-octatetraene identified by its uv spectrum.[45,46] After gas chromatography the product from the reaction in methanol 28 (R= $-CH_2OH$) still showed the same three uv peaks. The formation of the substituted hexatriene has been reported to be first order in the intensity of the exciting light by Migirdicyan and coworkers.[47-49] There is no evidence which allows the distinction between a four-centered reaction and one involving a hexatriene diradical.

Several groups have observed the esr spectra of solvent radicals upon irradiation of benzene in rigid glasses.[50-53] The esr spectra of the radicals from the 2537 A irradiation of benzene in the glass and esr spectra of the radicals produced by the γ-radiolysis of the pure solvent glass were the same. The formation of molecular hydrogen with a yield greater than twice the yield of radical formation was reported by Shelimov and coworkers.[51] The source of most of the hydrogen was the solvent since the use of benzene-d_6 led to a ratio of H_2/HD of 9.5 at benzene-d_6 concentration of $1.8X10^{-3}$ M and 8.1 at benzene-d_6 concentration of $6.0X10^{-2}$ M as determined by mass spectroscopy. The formation of both hydrogen and solvent radicals was reported to be second order in the intensity of irradiation.[50,52,53] The reaction is interpreted in terms of triplet benzene absorbing a second quantum of energy to produce a doubly excited triplet. The doubly excited triplet transfers its energy to a solvent molecule (RH = 3-methylpentane, methylcyclohexane, 2-methyltetrahydrofuran, methanol, isopropyl alcohol, or cyclohexane) producing ground state benzene and a solvent triplet which dissociates into two radicals, $H^{\cdot}$ and $R^{\cdot}$. The hydrogen radical abstracts a hydrogen from another solvent molecule and produces a second trapped solvent radical $R^{\cdot}$.[52] Support for the biphotonic process involving a doubly excited triplet comes from the recent observation by Godfrey and Porter[54] of the absorption spectrum of triplet benzene which was observed after flash photolysis of benzene in a rigid matrix at 77° K.

SUMMARY

Benzene irradiated in the vapor phase at wavelengths shorter than 2200 A produces polymer, fulvene, an unidentified intermediate, and decomposition products. Fulvene and benzvalene have been isolated from irradiated benzene solutions, and the presence of benzvalene and dewar benzene in solution has been detected by formal addition reactions to both benzvalene and dewar benzene. Two mechanisms have been proposed to account for the benzene photoreactions. The Bryce-Smith and Longuet-Higgins mechanism is based on the correlation of the lowest benzene singlet and triplet states with singlet or triplet states of diradicals which can lead to the observed products. The Farenhorst mechanism is based on a trans-benzene intermediate which has pi-orbitals topologically equivalent to a Moebius ring. In rigid media at 77° K benzene forms substituted hexatrienes by a monophotonic process and leads to the formation of solvent radicals and hydrogen by a biphotonic process.

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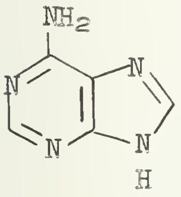
THE PHOTODIMERIZATION OF THYMINE

Reported by Sheldon A. Schaffer

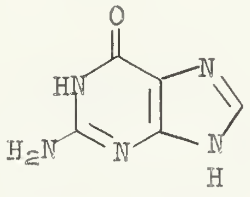
March 16, 1967

INTRODUCTION

It has long been hypothesized that ultraviolet (UV) radiation damage to microorganisms has involved alterations in the deoxyribonucleic acids (DNA) of the organism,[1] but until fairly recently a molecular interpretation of the radiation damage was unavailable. Since the UV spectrum of DNA is due almost entirely to the absorptions of its purine and pyrimidine base components, most of the investigations of UV photodamage have involved studies of the photochemistry of the most common purines, adenine (I) and guanine (II), and the most common pyrimidines, thymine (III), cytosine (IV) and uracil (V) (Note that thymine is found only in DNA and uracil is found only in ribonucleic acids (RNA)).



I



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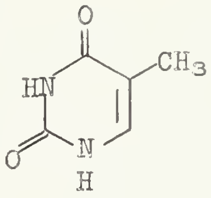

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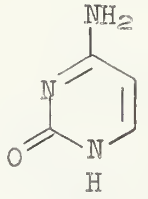

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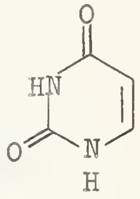


V

Early studied[2-4] indicated that the pyrimidine bases were much more sensitive to UV radiation than the purines, and therefore most investigations have been directed toward the photochemistry of the pyrimidines.

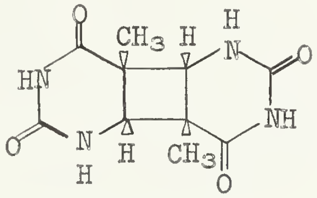
ISOLATION OF THE THYMINE PHOTODIMER

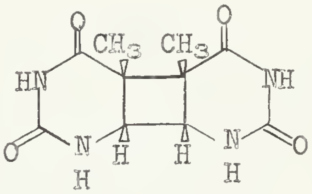
The first photoproduct isolated from UV irradiation of solutions of pyrimidines was the hydration product of uracil, 5,6-dihydro-6-hydroxyuracil.[2,5,6] Berends and co-workers[7] pointed out that the slow reversible hydration of uracil could not account for the rapid lethal effect of UV radiation on bacteria. Their investigations showed that besides the reversible hydration of uracil an irreversible reaction takes place when the irradiation is carried out on an aqueous solution at neutral pH. Later work on the irradiation of pyrimidine bases in frozen aqueous solutions showed that thymine, which exhibits only weak susceptibility to UV radiation in liquid aqueous solutions, was highly sensitive to such radiation in frozen solutions. Thus, irradiation of a frozen aqueous solution of thymine with a 4W germicidal lamp (with maximum intensity at 254 mμ) for 15 minutes resulted in a 40% loss of thymine absorptivity at 264 mμ. Uracil under the same conditions lost only 6% (corrected for the formation of reversible photoproduct) of its absorptivity at 260 mμ, while cytosine was totally unaffected. The reason for the not too obvious experiment of irradiation of frozen solutions of pyrimidines was that DNA in aqueous solution is known[9] to be surrounded by an ordered lattice of water, and it was thought that frozen aqueous solutions of the pyrimidine bases would approximate the native state of DNA better than liquid solutions and thus provide a better model for the investigations of the photochemistry of DNA.

Irradiations of DNA[10] and apurinic acid[11] (DNA which has undergone a mild acid hydrolysis to remove all the purine bases) gave products chromatographically identical to the so-called "first irreversible product"[7] obtained from the irradiation of thymine in frozen solutions.

Beukers and Berends[12,13] reported the first physical data on the thymine photoproduct. Their compound gave an elemental analysis for $C_5H_6O_2N_2$, the molecular formula of thymine, thus showing that it was either a dimer or polymer of thymine. A molecular weight determination by the method of isothermic distillation[14] gave values between 240 and 270 indicating that the molecule was a dimer of thymine (calc. mol. wt. = 252). The compound lacked UV absorption at 264 mμ, indicating the lack of the C_5-C_6 double bond of thymine, and its infrared spectrum showed weak peaks at 960 cm^{-1} which were taken to be characteristic of a cyclobutane ring system

(in the light of recent evidence[16] this assignment is somewhat in doubt). The nmr spectrum[17] (DMSO-d_6) showed signals (relative to external water) at -326 (2H, singlet, -NH), -179 (2H, singlet, -NH), +43 (2H, singlet, -CH), and +185 cps (6H, singlet, C-CH_3). On the basis of these data Beukers and Berends[13] suggested structure VI for the thymine photodimer. Wulff and Fraenkel[17] pointed out that there are four structures, VI-IX, which fit the data for the thymine photodimer.


VI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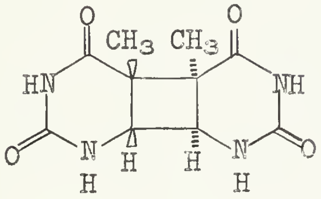
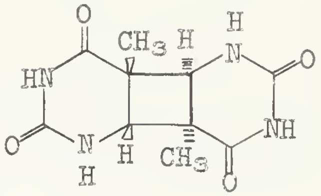
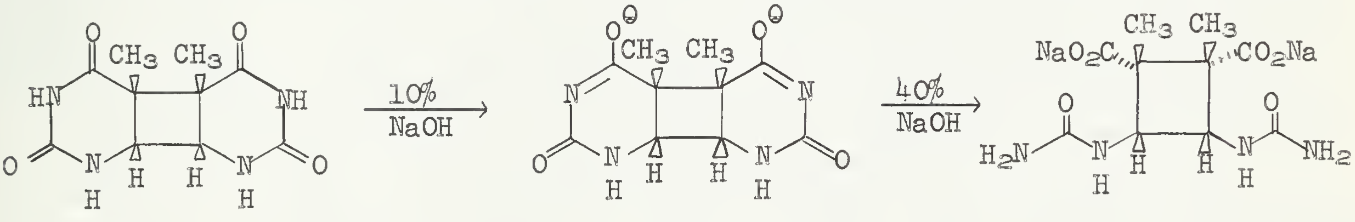

VIII


IX

They also showed that molecular models indicate that only the *cis-syn* isomer (VII) could reasonably be expected to be formed from the dimerization of adjacent thymines on the same DNA strand, and therefore the *cis-syn* structure should be assigned to the dimer isolated from DNA. An enzymatic digestion of a sample of UV irradiated DNA gave various trinucleotides of the type pXp$\widehat{TpT}$[17b] (where X is any one of the four bases occurring in DNA and $\widehat{TpT}$ is the thymine dimer joined by the normal phosphodiester bond between the ribose moieties of the thymine nucleosides). This implies that at least some of the thymine dimers are formed between adjacent thymines on the same DNA strand. Furthermore, they suggested that one of the *trans* isomers (VIII or IX) might be formed in cross-linked dimers between two DNA strands.[18,19]

THE STRUCTURE DETERMINATION OF THE THYMINE PHOTODIMER

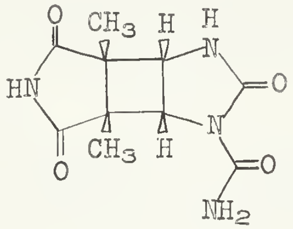
In 1965 Blackburn and Davies[20] offered the first chemical proof of structure for the thymine dimer. They found[20,21] that the treatment of the thymine dimer (formed by the irradiation of a frozen solution of thymine) with 10% NaOH gave a disodium salt believed to have structure X because it exhibited a maximum UV absorption at 237 mμ. The monoanion of thymine has its maximum absorption at 230 mμ. Increasing the NaOH concentration to 40% resulted in the formation of a white precipitate which showed only end absorption in the UV and whose IR spectrum showed bands at 1310, 1560 (CO_2^-), 1655 (-$NHCONH_2$), 3150, 3280 and 3370 cm^{-1} (amide NH's). This material was assinged the structure of the disodium salt of the bisureido acid (XI). Such ureido acids are known to be formed from 5,6-dihydrouracils by treatment with base.[22,23] When XI was dissolved in water it reverted to X, and X could be converted back to the thymine dimer by treatment with acid. The facile recyclization of XI in water is in contrast to the behavior of the β-ureido acid salts of the



X XI

5,6-dihydrouracils which recyclize only in the presence of acid[22,23] and is probably due to the all *cis* arrangement of groups on the cyclobutane ring.

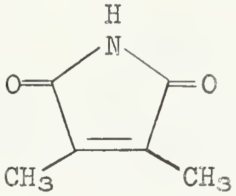
Treatment of XI with bromine (an attempted Hoffmann rearrangement) resulted in the formation of a rearranged product isomeric with the thymine dimer. This compound exhibited only UV end absorption in both alkaline and neutral solutions; its IR spectrum showed bands at 1674 ($NHCONH_2$), 1723, 1770 (CONHCO), 3240, 3370 and 3420 cm^{-1} (amide NH's); the nmr spectrum (in trifluoroacetic acid) gave signals at τ0.02 (1H, singlet, NH), 2.55 (1H, singlet, NH), 4.96 (1H, doublet, J = 9 cps, cyclobutane hydrogen), 5.55 (1H, quartet, J_1 = 9 cps, J_2 = 2 cps, cyclobutane hydrogen), 8.38 and 8.45 (3H each, singlets, $C-CH_3$). The weak coupling of the signal at τ5.55 could be eliminated by running the spectrum in deuterated TFA. In DMSO solution an additional broad band appeared at τ2.9 (2H, NH). On the basis of these data, Blackburn and Davies offered structure XII as the rearranged compound.



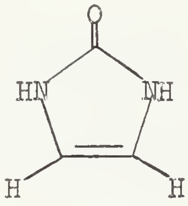
XII

The chemical proof offered to support structure XII is as follows: treatment of the rearranged product with nitrous acid results in the loss of the carbamoyl moiety with a simultaneous collapse in the nmr AB pattern to an A_2 system. This requires the location of the carbamoyl group on one of the nitrogens of the imidazole ring to provide the molecular dissymmetry which makes the cyclobutane hydrogens magnetically non-equivalent.

Pyrolysis of XII, or its decarbamoylated derivative, gave 2,3-dimethylmaleimide, XIII, and 2-imidazolone, XIV. The production of XIII shows that both the rearranged product and the thymine dimer had methyl groups on *vicinal* carbons, and therefore the dimer must have one of the *syn* structures VII or VIII. A *syn* structure is also indicated by the $J_{C_{13}H}$ satellite spectrum in the nmr of the dimer.[24]



XIII



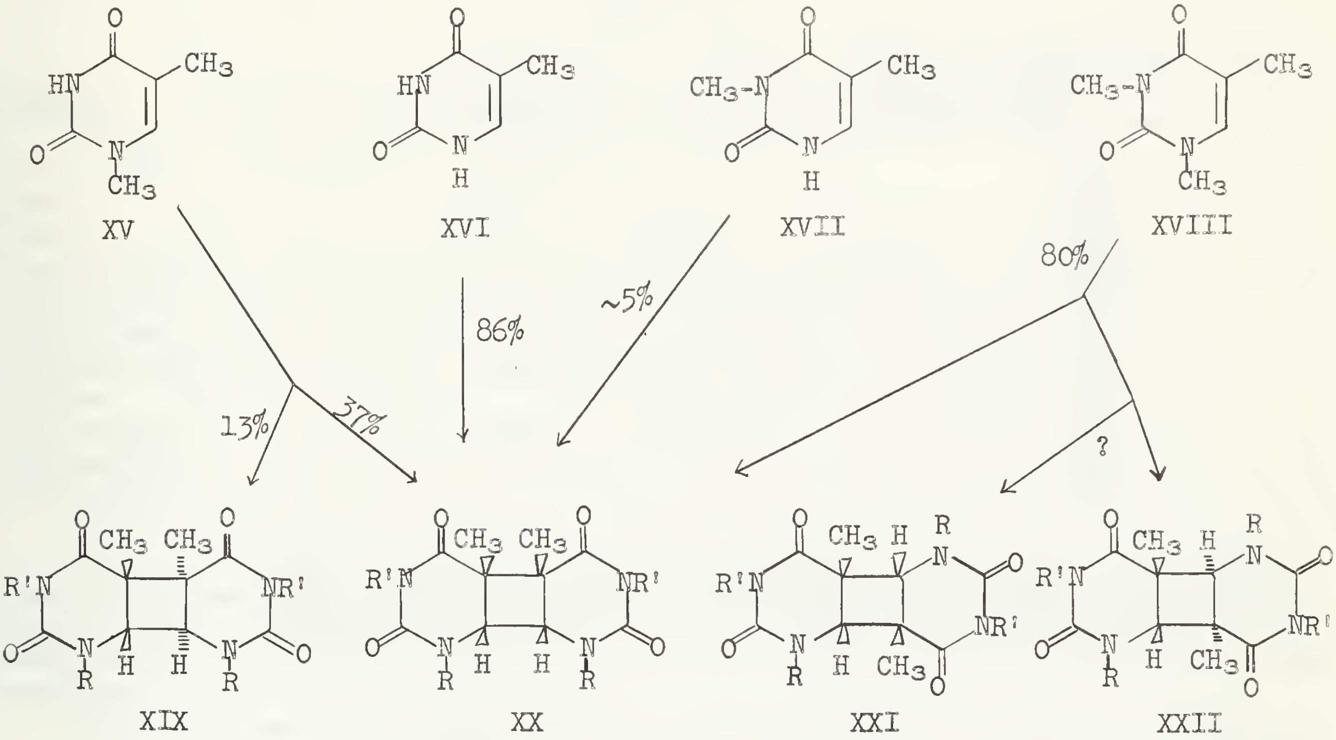
XIV

The formation of 2-imidazolone (XIV) from the pyrolysis, taken with the nmr data of XII, confirm that the cyclobutane hydrogens of the dimer were *vicinal*. The coupling constant of 9 cps for these hydrogens is consistent[25] with their being *cis* oriented, but their orientation cannot be rigorously proved in this way as the Karplus relation[26] is not strictly applicable to systems containing strong electronegative groups.[27] Further proof for the *cis* ring junction was based on the failure of similar systems to give *trans* fused rings[28] and the fact that only *cis* fused dimethyl bicyclo[4.2.0]octane-7,8-dicarboxylate gives cyclohexene on pyrolysis.[29]

Chemical proof of structure for the DNA derived thymine photodimer was obtained by Blackburn and Davies[30] by growing *E. coli* on thymidine-6T, irradiating the bacteria with UV light, and isolating the photoproducts chromatographically. The photoproducts were mixed with carrier thymine "ice-dimer" and repeatedly recrystallized without loss of any radioactivity. Treatment of an NaOH solution of the dimer with bromine gave the rearrangement product XII with 70% of the initial activity. Since Blackburn and Davies feel that the oxidative rearrangement is only allowed for the *cis-syn* isomer, they conclude that the DNA derived dimer must then have structure VII.

STUDIES ON SUBSTITUTED THYMINES

Studies on the UV induced photodimerizations of substituted thymines,[17,31] thymidine,[32] and thymidyl (3' → 5') thymidine[33] have shown that more than one cyclobutane type thymine dimer may be formed. The identification of the photodimers from substituted thymines has been presented by Blackburn and Davies[31] and rests on the following evidence: irradiation of a frozen solution of 1,3-dimethylthymine leads to two cyclobutane type photodimers[17] the higher melting of which was shown to be identical with the tetramethyl derivative of the thymine "ice-dimer",[17] and thus has structure XXb. Similarly, 1-methylthymine gives two cyclobutane photodimers when irradiated in a frozen aqueous solution.[31] Both of these photodimers are alkylated smoothly with dimethylsulfate to give the tetramethyl compounds. One of these compounds was shown to be identical to the tetramethyl derivative of the thymine "ice-dimer" and thus the original compound had structure XXc. The other dimethylated-derivative of the 1-methylthymine dimer was different from the unassigned, lower melting dimer from 1,3-dimethylthymine and thus represents a third isomer.



(a: $R=R'=H$)
(b: $R=R'=CH_3$)
(c: $R=CH_3, R'=H$)

(a: $R=R'=H$)
(b: $R=R'=CH_3$)
(c: $R=CH_3, R'=H$)
(d: $R=H, R'=CH_3$)

(a: $R=R'=H$)
(b: $R=R'=CH_3$)

(a: $R=R'=H$)
(b: $R=R'=CH_3$)

Blackburn and Davies pointed out that 1-methylthymine exists in two crystal modifications[34] and that topochemical arguments (*vide infra*) presented by Stewart[35] show that irradiation in the solid state of the more stable of the crystal forms should give the dimer XIXc. On this basis the second dimer of 1-methylthymine was assigned the *trans-syn* structure XIXc. This implies that the unassigned dimer from 1,3-dimethylthymine must have one of the *anti* structures, either XXIb or XXIIb. An assignment cannot be made for this compound at this time.

The structure of the photodimer of 3-methylthymine was deduced from the partial methylation of the thymine "ice-dimer" to give a symmetrical dimethyl derivative (determined by nmr) which undergoes photoreversion (*vide infra*) to 3-methylthymine and is identical in its spectroscopic and chromatographic properties with the 3-methylthymine dimer. This establishes structure XXd for the 3-methylthymine dimer.

Weinblum and Johns[32] have carried out a similar treatment to prove the structures of four different thymine dimers obtained from thymine, thymidine, DNA and

thymidyl (3' → 5') thymidine.

MECHANISM OF THE PHOTODIMERIZATION

Photodimerizations of the type undergone by thymine have been observed for other pyrimidine bases.[36-38] Wacker[38] has attempted to correlate the tendency of pyrimidines to undergo a photodimerization with the polarity of the C_5-C_6 double bond. Mantione and Pullman[39] have pointed out that this argument considers only the ground state properties of the molecules and does not take into account the role of the photoactivation. An alternate explanation based on the unpaired electron density in the C_5-C_6 double bond in the excited triplet state of the pyrimidines was offered by Mantione and Pullman to explain the relative order of dimerization of the pyrimidine bases.

The calculations of Mantione and Pullman, presented in Table 1, were made using simple Hückel molecular orbital theory. They acknowledge the fact that this simple theory does not distinguish between excited state singlets or triplets, but they assume that the calculations nearly represent the thymine triplet.

Table 1[39]

Compound	Ability to dimerize	Conc. of odd electrons in the C_5-C_6 bond in the excited triplet state.
Orotic acid	Good	1.120
Thymine	"	1.207
Uracil	"	1.252
6-Methyluracil	"	1.208
Isocytosine	Fair	1.159
5-Aminouracil	"	1.053
5-Methylcytosine	Weak	0.879
Cytosine	"	0.857
2-Thiothymine	Nil	0.953
5-Nitrouracil	"	0.639
6-Azathymine	"	1.142

The data in Table 1 show good qualitative agreement with experimental fact (except for those compounds which contain an additional heteroatom) and while the results indicate that high electron spin density in the C_5-C_6 bond promotes dimerization, they do not prove that the triplet excited state is a precursor to the photodimer.

The reason that the triplet state is favored by Mantione and Pullman seems to be linked to the observation by Beukers and Berends[7,37] that oxygen and paramagnetic salts decrease the production of photoproducts in the irradiation of liquid solutions of uracil and increase the amount of photoreversion of previously formed dimers. It is known that paramagnetic substances increase the number of singlet → triplet transitions allowed by increasing the spin-orbit coupling in the molecules undergoing the transitions.[40]

Recently Lamola and Mittal[41] have studied the dimerizations of thymine and uracil in acetonitrile. They found that the dimerization of thymine could be completely quenched by the addition of isoprene (a triplet quencher for thymine). The uracil dimerization was only partially quenched by isoprene. This work implies that the dimerization of thymine in acetonitrile proceeds entirely through a triplet state while the dimerization of uracil proceeds partially through a triplet. Chromatographically the dimer formed from thymine in acetonitrile is different from the thymine "ice-dimer" and was tentatively assigned a trans-anti structure.

Lamola and Mittal also investigated the UV irradiation of uracil in liquid aqueous solution. The major products formed from such irradiations are the uracil hydration product and uracil dimers. Upon adding 2,4-hexadienol (HDE), an H_2O soluble triplet quencher, to the solution, they observed an increase in the ratio of hydrate to dimers. They could identify two dimers among the photoproducts, one of which was identical with the uracil "ice-dimer" while the other was a new dimer.

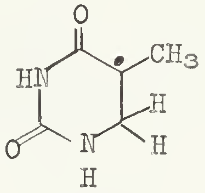
In the presence of HDE the ratio of "ice-dimer" to new dimer increased. Thus it appears that the new uracil dimer is formed through a triplet species while the uracil "ice-dimer" and the hydration product are not.

An analogous situation occurs in the dimerization of coumarin[42] where singlet state excited coumarin is thought to lead to a cis-"head-to-head" dimer while triplet excited coumarin gives the trans-"head-to-head" and "head-to-tail" dimers.

Dönges and Fahr[43] have recently studied the structure of the uracil "ice-dimer" and have assigned to it a cis-"head-to-head" structure. Thus it appears that the dimerization of uracil in liquid aqueous media is controlled in the same way as the dimerization of coumarin, and the dimerization of thymine in liquid solutions may be under this same control.

Excited state triplets have been observed both by optical[44] and ESR[45,46] measurements on UV irradiated thymine and DNA samples in H_2O:ethylene glycol glasses at 77°K. The triplet species found in all the cases studied could be assigned to the conjugate base of thymine.

Free radicals have also been in UV irradiated samples of thymine and DNA[47-49] at 77°K, and here again the radical could be assigned to a thymine species, XXIII.

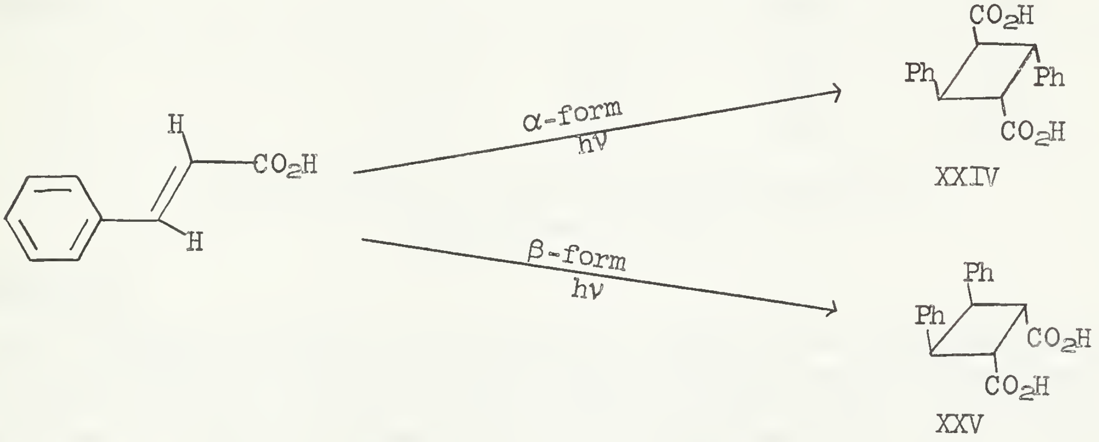


XXIII

These data show that the thymine triplet and free radical are important species present in UV irradiated samples of thymine and DNA, but they do not implicate either species directly in the photodimerization reaction.

CONTROL OF THE STEREOCHEMISTRY OF THE THYMINE "ICE-DIMER"

It was mentioned above that one of the isomeric dimers obtained from the irradiation of a frozen solution of 1-methylthymine was assigned its structure on the basis of the crystal structure of 1-methylthymine.[35] Schmidt and co-workers[50] have shown that the photodimerizations of olefins in the solid state depends on the orientation of the molecules in the crystal lattice and occur with a minimum amount of atomic and molecular motion. Among the examples of this topochemical control is the dimerization of trans-cinnamic acid. This compound exists in two crystal forms, α and β. Irradiation of the more stable, α, form gives only α-truxillic acid, XXIV, while irradiation of the β form leads only to β-truxinic acid, XXV.[51,52]

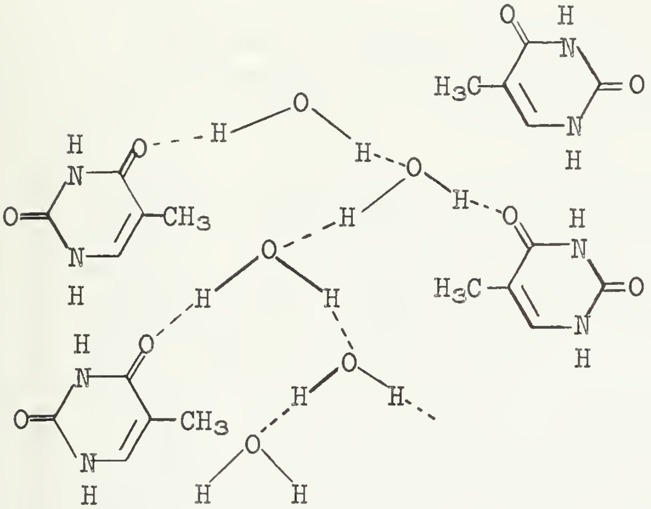


Wang[53-55] has suggested that thymine in frozen aqueous solutions exists in a high state of aggregation, being excluded from the ice crystals and forced into clusters of solid thymine. The UV spectrum of thymine in a frozen solution[56] most nearly resembles the spectrum of solid thymine and helps to confirm Wang's theory.

If thymine does exist in a high state of aggregation in a frozen solution, then the arguments of Schmidt and his co-workers[55] would require that the stereochemistry of the dimer formed from the UV irradiation of the frozen solution should be determined by the crystal structure of solid thymine.

An X-ray analysis of thymine monohydrate[57] shows it to have a structure which can be represented as in Figure 1. If we restrict the photodimerization of thymine to that course which requires the least amount of molecular movement, it is clear that the cis-syn isomer will be the only dimer formed. Evidence that thymine exists as the monohydrate in frozen aqueous solutions comes from experiments by Wang[58] where thin films of thymine were irradiated under conditions of varying humidity. Table 2 illustrates the importance of humidity on the thymine dimerization, and Wang regards these data as proof that thymine monohydrate is the species undergoing the photodimerization.

Figure 1



Crystal Structure of Thymine Monohydrate[58]

Table 2

	Humidity (%)			
Time (hr)	98	71	30	P_2O_5
1	15.0	17.3	11.4	7.5
2	31.0	30.9	21.0	16.3
3	55.0	55.0	27.0	21.7

% Dimerization of Thymine Under Conditions of Varying Humidity(58).

PHOTOREVERSION

One of the major reasons for the interest shown in the photodimerization of thymine is its connection with the biological inactivation of bacteria and phages by UV light.[19,59-63] It has been well established that some of the effects of UV radiation may be reversed by some photochemical process,[64] and one of the first properties of the thymine photodimer to be determined was its ability to revert back to thymine when it was reirradiated with UV light in a liquid aqueous solution. In fact, it was shown that irradiation of thymine led to the establishment of a photostationary state between the photodimer and the monomer.[65] At short wavelengths the equilibrium favors the monomer while long wavelengths favor the dimer.

It has also been found that a crude enzyme extract from yeast catalyzes the splitting of the thymine dimer[63,66] or the splitting out of the dimer from the DNA chain.[67]

The thymine dimer now has a firmly established place in the area of photo-damage and photorepair in biological systems.

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THERMAL REARRANGEMENTS OF CYCLOHEPTATRIENES[1]

Reported By W. D. Shermer March 20, 1967

Introduction:

Cycloheptatrienes, which also have the common name tropilidenes, have been found to undergo several thermal and photolytic rearrangements. These isomerizations can be divided into two genral classes - hydride shifts and skeletal rearrangements. The latter rearrangements are exemplified by the reactions shown in Figure 1. One example of the photochemical rearrangements will be discussed briefly but it is not intended to be a complete review.

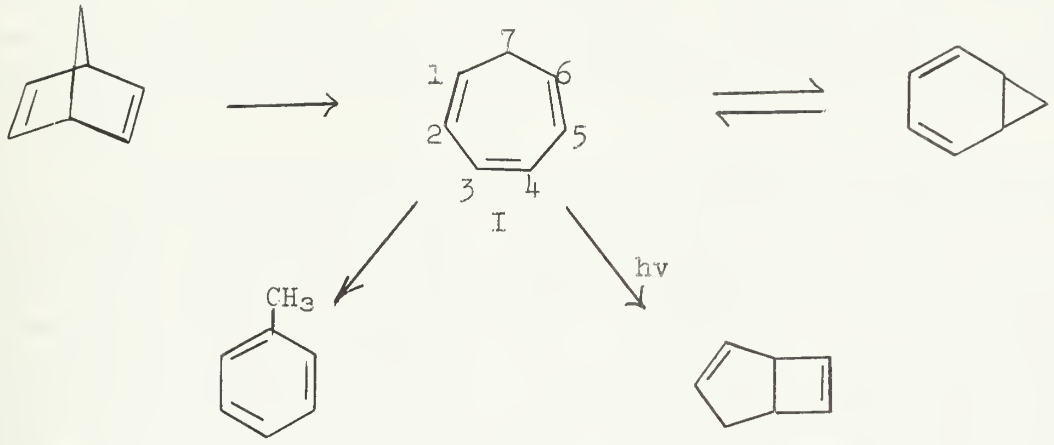
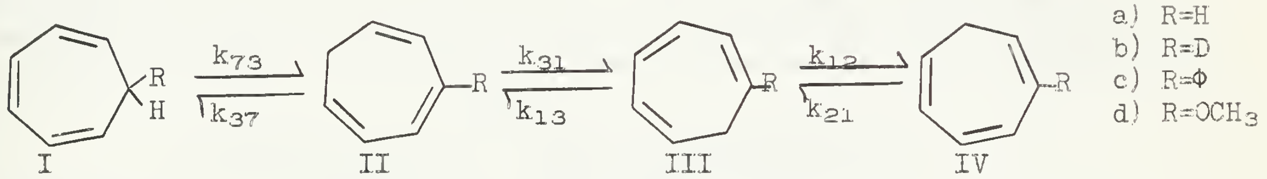


Figure 1

Hydride Shifts:

(Eq. 1)



Chemical studies involving thermal reactions of 7-substituted cycloheptatrienes have often been complicated by the production of unexpected side-products resulting from the isomerization of the substituted tropilidene.[2,3] This isomerization could conceivably occur by either an intermolecular or an intramolecular process or both. Since equation 2 is a known reaction,[4] a possible intermolecular reaction would be the initial formation of a small amount of tropylium ion, followed by hydride-ion transfer from another cycloheptatriene molecules.[3] To distinguish between the inter- and intramolecular processes, ter Borg and his coworkers undertook a study of 7-deuterocycloheptatriene (I-b) by mass spectroscopy. Table 1 gives the results of their work. The invariance of the isotopic distribution over the range of experimental conditions rules out the possibility of an intermolecular rearrangement.

(Eq. 2)

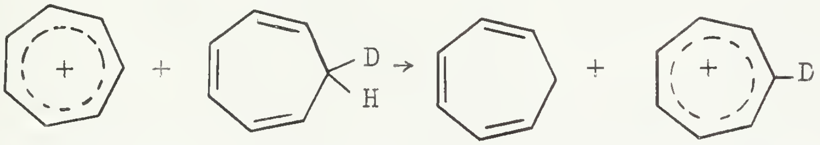


Table 1
Distribution of Deuterium After Heating 7-Deuterocycloheptatriene
(percentages)

	Starting Material	Heated Products					Calculated Binomial Distribution Due To Intermolecular Reaction
Temperature °C		98	98	121	140	140	
Time hours		1700	3297	449	270	412	
C_7H_8	6.0	6.1	5.9	6.0	6.2	6.1	36.8
C_7H_7D	93.9	93.9	94.1	93.9	93.7	93.8	39.2
$C_7H_6D_2$	0.1	-	-	0.1	0.1	0.1	18.3
$C_7H_5D_3$	-	-	-	-	-	-	4.9 + D_4, D_5,etc.

Four intramolecular shifts are possible: (1) from C-7 to C-1 or C-6 (α position), (2) from C-7 to C-2 or C-5 (β position), (3) from C-7 to C-3 or C-4 (γ position), and (4) a random shift from the 7 position to the α, β, and γ positions. To elucidate which of the four possible mechanisms is in operation, Nozoe and Takahasi[2] followed the isomerization of 7-methoxycycloheptatriene. The peaks in the NMR spectrum due to the methyl and C-7 protons (6.65τ and 6.83τ respectively) decrease with time at 103°C and eventually disappear completely. Simultaneously, a singlet at 6.43τ(3H) and a triplet at 7.77τ(2H) appear and increase in intensity. On continued heating, a singlet at 6.50τ(3H) and a doublet at 7.55τ(2H) appear and increase in intensity and, on prolonged heating, increase at the expense of the signals at 6.43τ and 7.77τ. As equilibrium nears, two new signals appear, a singlet at 6.58τ(3H) and a triplet at 7.83τ(2H). At equilibrium the areas under the methyl peaks is as follows: 6.43τ:6.50τ:6.58τ=13.6:80.5:6.0. Analysis of the four proposed mechanisms shows that only the 7 to γ hydride shift will give the sequence of peaks observed for the C-7 hydrogens of multiplet - triplet - doublet - triplet.

A. P. ter Borg and coworkers[3] made a kinetic study of the isomerization of I-b. It was noted that a shift of a deuterium atom from the 7 position yields the same compound and, consequently, no first order isotope effects are observed. Neglecting second order effects, which are generally small, only one rate constant is involved in the reactions. This constant is defined as the rate constant for the reaction in which a hydrogen of the CH_2 group shifts, i.e. $k_{73}=k_{37}=k_{31}$ etc. (for I-b a statistical factor of 1/2 is necessary). Differential rate equations were developed to describe the rearrangements taking place for the 7 to γ shift as well as for each of the other three possible mechanisms. Theoretical calculations, based upon the experimentally determined number of hydrogens in the 7 position and the length of time of heating, were carried out to determine the number of protons in the α, β, and γ positions. These calculated values were then compared to the experimental values to determine which mechanism best fit the experimental data. Table 2 gives the results of one such set of calculations. For broad peaks, the error in integration of NMR spectra can be as high as 10%, decreasing as the peaks get sharper and more intense.[7] No mention is made in the paper of what was done to minimize this error. Consequently, the significance of these numbers is in doubt and the tables can not be accepted at full face value. In their NMR studies, ter Borg and Kloosterziel found the same sequence of signals, mentioned above in Nozoe's work, develop for the proton in the 7 position in I-b and ter Borg cites this as evidence for the 7 to γ shift. The data given in Table 2 appear to substantiate this conclusion, but a more positive statement cannot be made. In accordance with the 7-γ hydrogen shift, ter Borg proposed the mechanism shown in Figure 2. The multicentered, intramolecular nature of the mechanism is further substantiated by an absence of solvent effects on the rates of rearrangement.

Table 2

Proton Distribution for 7-Deuterocycloheptatriene

(After heating at 140°C for 412 hours)

Position	Experimental	Calculated For Mechanism			
		7→γ	7→β	7→α	7→Random
7	1.66	(1.66)	(1.66)	(1.66)	(1.66)
α	1.82	1.81	1.86	1.73	1.80
β	1.86	1.86	1.73	1.81	1.80
γ	1.72	1.73	1.81	1.86	1.80

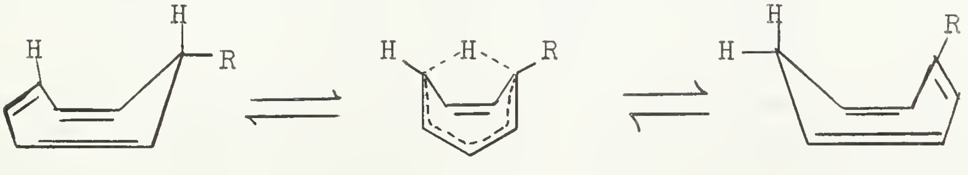


Figure 2

The rate constant for the isomerization of I-b, calculated from the observed number of protons in the 7, α, β, and γ positions, was $k=6.0 \times 10^{-7}$ sec^{-1} at 121°C. It has been observed that the rearrangement of I to II is always accelerated by substitution. For I-d at 121°C, Nozoe and Takahasi[2] found $k_{73}=2.48 \times 10^{-5}$ sec^{-1} (extrapolated), approximately 100 times as fast as the unsubstituted tropilidene. At 120.2°C, Nozoe reports $k_{73}=2.31 \times 10^{-5}$ sec^{-1} (extrapolated) for I-d and ter Borg reports $k_{73}=3.60 \times 10^{-5}$ sec^{-1} for I-c,[6] 7-phenylcycloheptatriene. The rate constants reported for I-d were based on NMR measurements and, since no standard deviation is reported, these numbers should be qualified in the same manner as the NMR work by ter Borg. The rate constant for I-c was based on UV measurements and should be quite accurate but, again, no standard deviation is reported.

Further information on these three compounds may be gained by comparing their activation parameters (Table 3). These values are based on NMR calculations with no standard deviation given and, therefore, can only be taken as approximate values. The large negative $\Delta S^{\pm}$ indicates that this reaction may proceed through a transition state such as that pictured by ter Borg. The decrease in activation energy in going from I-b to I-c possibly reflects the amount of conjugation energy due to the trienic and aromatic systems in the transition state. If this conjugation exists, it would require some co-planarity between the phenyl group and the trienic system in the transition state. This should result in a more negative $\Delta S^{\pm}$, which is observed experimentally. Nozoe ascribes the more negative $\Delta S^{\pm}$ for I-d as compared to I-c to some contribution of the lone pair of electrons to the ragidity of the transition state. However, Nozoe is trying to explain an extremely small difference between two numbers, of which only the value for I-c can be considered significant since it is based on UV measurements and not on NMR data as is the $\Delta S^{\pm}$ for I-d. Consequently, this explanation is highly speculative and, as Nozoe admits,[2] more work is necessary. This same problem exists in trying to explain the $\Delta\Delta S^{\pm}$ for I-b and I-c. While the difference can only be regarded as the approximate value, when considered in the light of the mechanism proposed by ter Borg and the values of the Arrhenius activation energies, it is at least indicative of the difference which does exist between the two entropy values.

Table 3

Activation Parameters

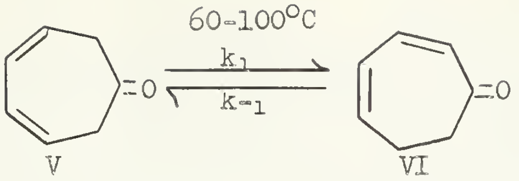
Compound	ΔE_a(Kcal./mole)	$\Delta H^{\pm}$(Kcal./mole)	$\Delta S^{\pm}$(e.u.)
I-b[3]	31	30.2	- 8.2
I-c	27.6	26.9	-11.7
I-d[9]	26.4	25.7	-15.0

The equilibrium concentrations of a series of R groups was studied by ter Borg and coworkers. In compounds III, II, IV, and I the R group is in conjugation with 3, 2, 1, and 0 double bonds of the trienic system respectively and their respective concentrations reflect the ability of the isomer to be stabilized through conjugation as the electron donating tendency of R increases, isomer III predominating. If R is other than an electron-donating group, no overwhelming preference of one isomer over another is shown.

Equilibrium Concentrations[8]

R	III	II	IV	I	T °C
$N(CH_3)_2$	100	--	--	--	100
OCH_3	88	9	3	--	120
SCH	76	16	8	--	114
CH_3	57	24	17	2	140
C_6H_5	64	18	18	--	136
CN	52	24	24	--	142

The mechanism proposed by ter Borg for the rearrangement involves a 1,5 hydrogen shift with migration of two double bonds, the remaining double bond not participating. If this hypothesis is true, 1,3-cycloheptadienes should also undergo rearrangement. Kloosterziel and ter Borg[10] prepared 2,7-dihydrotopone (V) and

(Eq. 3) 

found that it rearranged to 2,3-dihydrotropone (VI). The rate of isomerization was followed via UV and the equilibrium constant calculated. At 60°C, $K=k_1/k_{-1}=1.86$; $k_1=1.42\text{x}10^{-6}$ sec^{-1} and $k_{-1}=7.6$ x 10^{-7} sec^{-1}. These rate constants include no significant solvent effect: at 60°C $k_1 + k_{-1}=2.18$ x 10^{-6}sec^{-1} in n-heptane and 4.5 x 10^{-6}sec^{-1} in ethanol. The slight solvent effects which do appear may be due to the solvation of the carbonyl group. At 101°C, $k_1=1.16$ x 10^{-4}sec^{-1} or approximately 10^4 times k_{73} for tropilidene itself. There is no spectral evidence for the presence of an enol and, therefore, a maximum of only a few percent may be present. As a result, formation of the enol and subsequent hydride transfer is ruled out by ter Borg, who proposes that the small amount of enol which might be formed would be insufficient to account for the large rate enhancement. Without knowing any rate data for the enol, this is not a well-grounded assumption. If the rate of reaction of the enol was very rapid, in conjunction with a steady state approximation, a few percent enol could easily account for the rate enhancement. It would be necessary to show that enolization catalysts, such as acids, do not affect the rate of reaction to prove that enolization does not cause the rate enhancement.

The predictions of Woodward and Hoffmann[11] also support the 1,5 hydride shift. Due to the constraints imposed by the ring, suprafacial hydride shifts are the most likely transfer mechanism and, thermally, only the 1,5 shift would be allowed to proceed in a suprafacial manner; the 1,3 and 1,7 shifts would be antarafacial. On the other hand, photochemically, the 1,3 and 1,7 shifts are allowed to be suprafacial and the 1,5 shift would be allowed in an antarafacial manner. Razenberg and ter Borg[12,13] found that the 7-substituted tropilidenes do indeed undergo a 1,7 shift in photolytically induced rearrangements. Thus all the work carried out substantiates the proposed 1,5 hydride shift in thermal isomerizations.

Skeletal Reorganizations:

A) Norbornadiene-Cycloheptatriene Isomerization

W. G. Wood[14] studied the isomerization of norbornadiene to form cycloheptatriene and found that toluene and the products of the reverse Diels-Alder reaction, acetylene and cyclopentadiene, were also formed. The mechanism shown in Figure 3 was considered because small amounts of benzene and ethylene were found as side-products and carbene is known to add to benzene to give tropilidene and toluene.

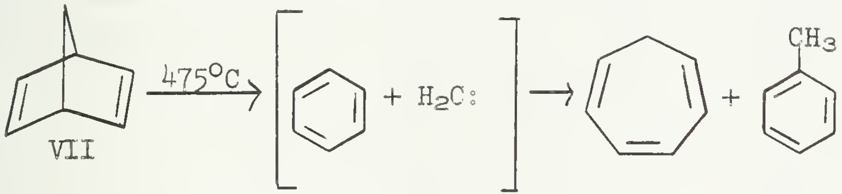


Figure 3

The norbornadiene was pyrolysed in the presence of a large excess of n-butane in an attempt to trap the carbene. However, no trace of pentanes or benzene were found while the isomerization and the reverse Diels-Alder proceeded to give the expected yields. Two controls were run to demonstrate that carbene does react, under the experimental conditions, with n-butane to give pentanes and with benzene to give toluene. Wood, therefore, concluded that this was not the correct mechanism and proposed the mechanism shown in Figure 4.

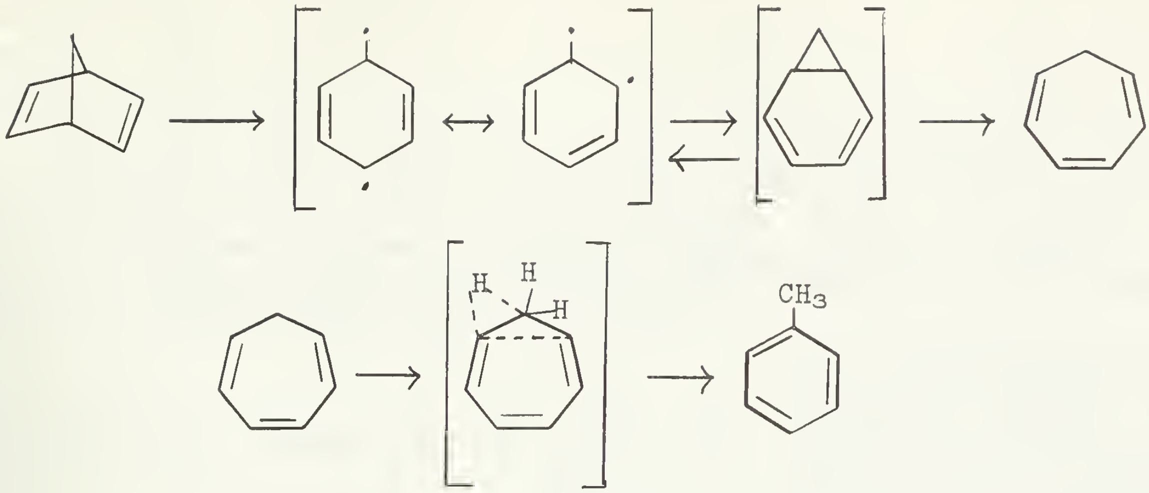
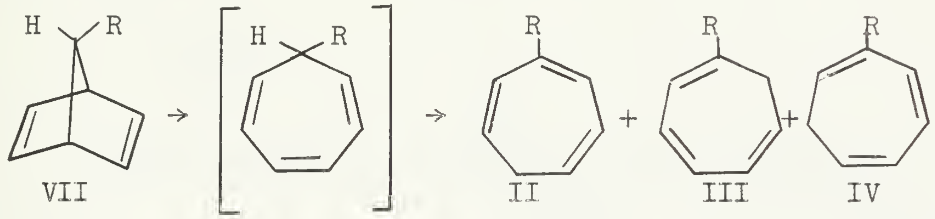


Figure 4

Lustgarten and Richey[15] studied the rearrangement of 7-phenyl and 7-alkoxy-norbornadienes to cycloheptatrienes and found only the 1, 2, and 3-substituted tropilidenes, no aromatic isomers where found. No significant solvent effects were observed which tends to rule out charge separation in the transition state and indicates that an intramolecular process is possible.

(Eq. 4)

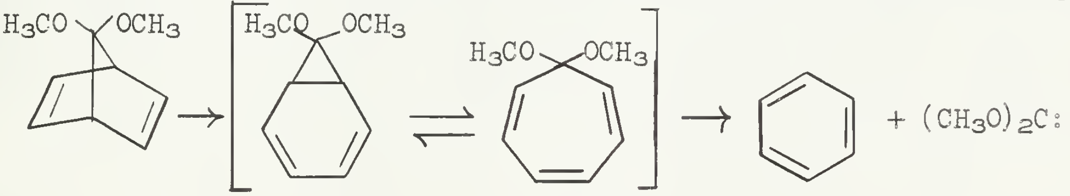


a) R=H
b) R=D
c) R=Φ
d) R=OMe
e) R=$OC(CH_3)_3$
f) R=$OC_2H_4OC_2H_5$

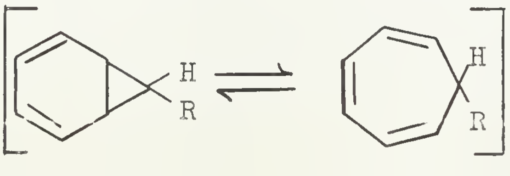
(In n-decane: $\Delta H^{\pm}=34.5$ Kcal./mole, $\Delta S^{\pm}=1$ e.u. for VII-e)

When R=H, the isomerization occurred at 475°C and toluene, cyclopentadiene, and acetylene were produced as well as tropilidene. When R was phenyl or alkoxy, the isomerization was carried out at only 175°C and only the substituted tropilidenes were observed. In contrast, when the methylene carbon had a ketal or thioketal substituent attached to it, the isomerization, which can be carried out in the same temperature range, produced only benzene and compounds derived from the ketal or thioketal function and no tropilidenes were found. Using a capillary furnace mounted at the inlet of a mass spectrometer, Lemal and coworkers[16,17] detected the presence of $\cdot CH_3$, CO_2, and $CH_3CO_2CH_3$ when 7,7-dimethoxynorbornadiene was pyrolysed. They proposed that benzene and dimethoxy carbene were initially produced and the carbenes then decomposing by a radical chain mechanism to give the products observed. To account for the formation of benzene and the dimethoxy carbene in a manner consistent with a general mechanism for the various substituted norbornadienes discussed above, Lustgarten and Richey proposed the intermediate shown in equation 5. Using this general mechanism, the equilibrium shown in equation 6 should exist for the monosubstituted norbornadiene but the fragmentation

(Eq. 5)



(Eq. 6)



of the norcaradiene intermediate would result in a less stable carbene than in the dimethoxy case and, therefore might be slower than the competing 1.5-hydrogen transfer. However, direct loss of dimethoxy carbene without intermediates cannot be ruled out, and since tropilidenes are not known to decompose to give carbenes, Lustgarten and Richey have no evidence for the intermediates in equation 5.

Herndon and Lowry[18] studied the kinetics of the isomerization of norbornadiene to cycloheptatriene to determine if the toluene produced was generated directly from the norbornadiene or from the cycloheptatriene or both. (See Figure 5.) They used a gas phase stirred flow reactor designed so that the contents of the reactor are completely mixed by diffusion, thereby leading to uniform concentrations which become time-invariant within the reactor.

The experimental results show that toluene is produced from both compounds. This result was indicated in some previous work by Klump and Chesick[19] but not proven conclusively. Table 4 gives the data obtained by Herndon and Lowry.

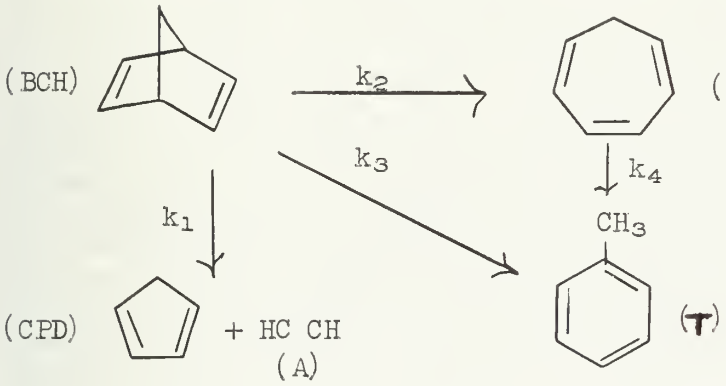


Figure 5

Table 4
Rate Constants and Arrhenius Activation Energies

	k (sec^{-1}) (400.6°C)	ΔE_a (cal./mole)
(1) BCH → CPD + A	2.31×10^{-2}	50,190 ± 760
(2) BCH → CHT	1.73×10^{-2}	50,610 ± 780
(3) BCH → T	1.04×10^{-3}	53,140 ± 730
(4) CHT → T	1.05×10^{-3}	52,100 ± 820

Herndon and Lowry claim all of the reactions are first order and unimolecular and present the reaction scheme shown in Figure 6 as the most likely mechanism. The symbol [I] represents a common intermediate to tropilidene and toluene. Birely and Chesick[20] have also examined these reactions and have obtained almost identical values for the various rate constants and energies of activation. Since the values of the activation energies for all of the equations in Table 4 are almost identical, Birely and Chesick claim that this is evidence for a common intermediate to all three products: cyclopentadienes (+ acetylene), cycloheptatriene, and toluene. Herndon and Lowry[18] dispute this conclusion and argue that this is evidence against a common intermediate and is evidence only for similar initial steps. If a common intermediate for the reverse Diels-Alder reaction and the isomerization did exist, the ratio of the rate constants can be shown to be the ratio for the reactions which take place after the common intermediate is formed. An Arrhenius plot of this ratio gives the difference in activation energies. In this case the difference is extremely small, 400 cal., and this would indicate that the two processes occurring after the intermediate is formed are essentially similar. But the isomerization and reverse Diels-Alder reactions are not similar. Thus, no common intermediate exists and it is simply fortuitous that the activation

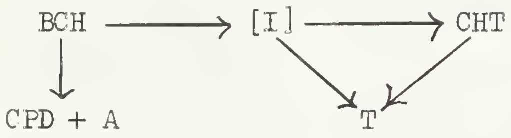


Figure 6

energies are almost identical. Using this same approach, it might also be argued that the similarity of the activation energies after the common intermediate is fortuitous, thereby allowing no distinction to be made. Tropilidene has not, as yet, been reported as a side product in the Diels-Alder synthesis of norbornadiene as might be expected if a common intermediate did exist and this has been offered in support of the theory of Herndon and Lowry. However, based upon the difference in the heats of formation,[35,36] formation of norbornadiene is favored by approximately 8 Kcal./mole and, consequently, it may be formed with complete exclusion of topilidene.

B) Norcaradiene - Cycloheptatriene Isomerization:

Some chemical reactions of tropilidene often give products which appear to come from norcaradiene,[19,21] while others give products involving the cycloheptatriene structure. This ambiguous nature would make it appear that tropilidene is in equilibrium with its valence tautomer - norcaradiene.

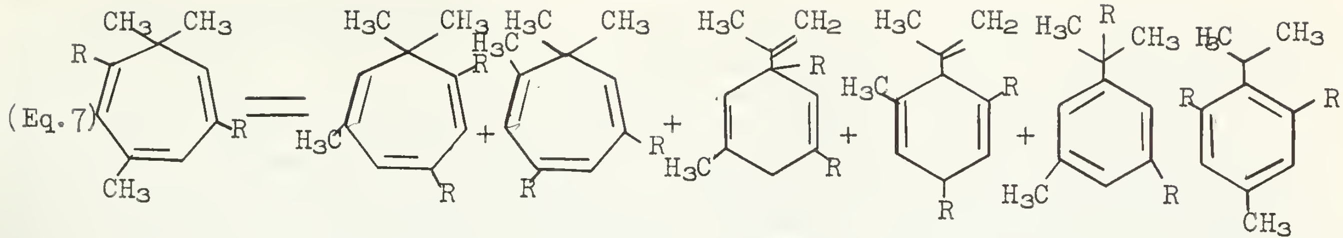
Anet[22] studied the temperature dependent NMR spectra of tropilidene to determine if it is planar or nonplanar. At -150°C, the methylene protons give rise to two chemically shifted bands with a separation of 76 cps and increasing. The mean chemical shift is 7.8τ, essentially unchanged from that observed at higher temperatures. Since the methylene protons are nonequivalent at low temperatures, cycloheptatriene is nonplanar. In similar work, Jensen and Smith[23] were able to get down to -170°C and the separation between peaks was 86 cps. They were not able to find any evidence for the presence of norcaradiene. An electron diffraction study by Traettenberg[24] showed that tropilidene was indeed nonplanar with the plane comprised of the 1,2,5, and 6 carbons making an angle of 36.5° with the plane of the 1,6, and 7 carbons and an angle of 40.5° with the plane of the 2,3,4, and 5 carbons.

An equilibrium between tropilidene and norcaradiene should be detected by variations in the coupling constants with changes in temperature. Roberts and coworkers[25] carried out a complete analysis of cycloheptatriene at -70°C and +115°C but no change in coupling constants could be observed. Consequently, there is less than 5% norcaradiene present even at -70°C. When 7,7-bistrifluoromethylcycloheptatriene was studied,[25] the trifluoromethyl groups remained equivalent down to -185°C and there is no evidence of any of the norcaradiene structure.

Both the trifluoromethyl group and the cyano group are strongly electron withdrawing, having negative resonance effects and negative inductive effects.[26] The Hammett para-sigma constants are 0.54 and 0.66 respectively.[27] Yet, when one of the CF$_3$ groups is replaced by a CN group, some norcaradiene is observed.[28] At -85°C, the relative concentration of the substituted tropilidene to substituted norcaradiene is 80:20 as calculated from NMR spectra peaks. When both trifluoromethyl groups are replaced by cyano groups, only the 7,7-dicyanonorcaradiene (VIII) is observed.[29] At 100°C, VIII rearranges to phenylmalonitrile and 3,7-dicyanocycloheptatriene (IX) which in turn undergoes a series of 1,5 hydrogen shifts to give 1,4- and 1,5-dicyanocycloheptatriene upon further heating.

C) 7,7-Disubstituted Cycloheptatrienes:

Berson and Willcott[3-32] examined the norcaradiene-diradical intermediate equilibrium proposed by Wood (Fig. 4) in an attempt to determine if the rate of recyclization of the diradical intermediate to form norcaradiene occurred at a rate competitive with hydrogen transfer to form toluene from the diradical intermediate. Blocking the 1,5-hydrogen transfer by disubstitution at the 7 position, 3,7,7-trimethyltropilidene (X) was pyrolysed at 300°C to produce the profusion of products shown in equation 7; the percentages given refer to the composition of the reaction mixture after pyrolysis for 40 minutes, but do not include 1 - 2% of unidentified products.



X(35%) XI(25%) XII(2%) XIII(20%) XIV(16%) XV(2%) (XVI)(2%)

a) R=H b) R=D

The mechanism of the isomerization has been shown by deuterium labeling to be a true skeletal rearrangement of the ring carbons rather than a superficial series of hydrogen shifts. Examination of equation 7 shows that the 1-6 carbon chain maintains the same sequence in each compound, while the C-7 carbon and its geminal methyls are allowed to wander and reattach between any pair. Both nonaromatizing rearrangements to form XI and XIV are reversible. When either XI or XIV is isolated and resubjected to the reaction conditions, a typical mixture of pyrolysis products results. Mass spectroscopy studies have shown that the rearrangements do not take place by an intermolecular process. The mechanism shown in Figure 7, proposed by Berson and Willcott,[32] incorporates the major structural changes, the intramolecularity, and the reversibility. This mechanism indicates that compounds XVII, XVIII, and XIX should be formed. So far these products have not been found but may be present in the 1-2% of unidentified material or may be formed after a longer period of time than Berson and Willcott ran their

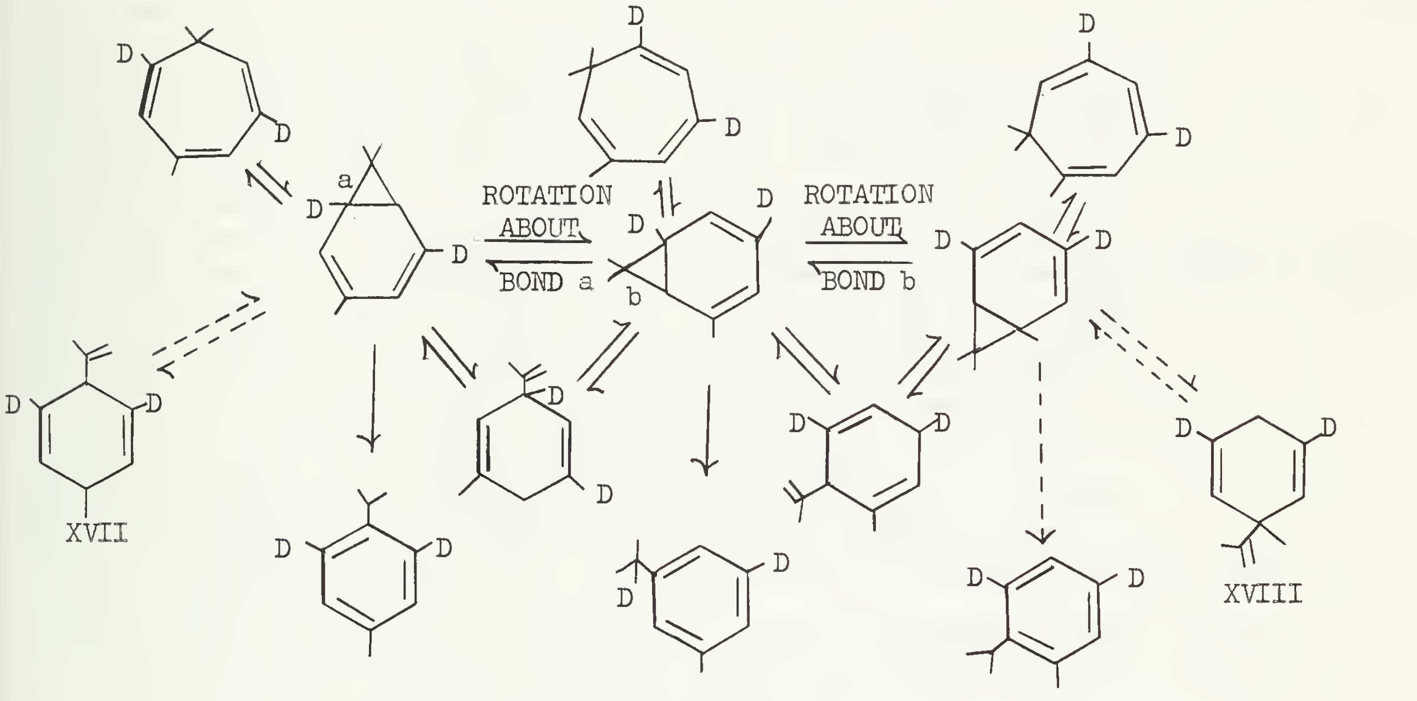


Figure 7

experiments. Production of the dienes XIII and XIV is not without precedent. Employing the norcaradiene intermediate, this isomerization can be classified as a Cope type rearrangement with one double bond being replaced by a cyclopropyl ring and a hydrogen from one of the geminal methyls being transfered to the six member ring.[37,38] There is no way to distinguish a diradical mechanism from a concerted 1,5-carbon shift without intermediates. This latter process is permitted, but not required,[11] and requires the C-7 migration from C-1 to C-5 to be suprafacial. An examination of properly substituted optically active tropilidenes should distinguish this from an antarafacial process and from a mechanism involving a diradical intermediate. This work is currently in progress.[32]

Photochemical Isomerization:

Chapman and Borden[33] found that irradiation of neat 7-alkoxycycloheptatriene produced mainly the substituted bicyclo[3.2.0]heptatriene (XX-b') and only trace amounts of toluene. If this irradiation is carried out in the vapor phase, both XX-b' and 1-alkoxycycloheptatriene (III-b') are produced. Pyrolysis of XX-b' produces III-b' and irradiation of III-b' converts it to XX-b'. Srinivasan[34] found that irradiation of tropilidene in the vapor phase produces mainly toluene and a maximum of 5% bicyclo[3.2.0]heptadiene (XX-a). The formation of neither toluene nor XX-a was quenched by addition of oxygen or nitric oxide, which indicates that the isomerization is intramolecular and that it does not arise from a triplet state of tropilidene. Srinivasan has postulated that toluene is formed from a vibrationally excited ground state and not from an upper electronic state. The production of the isopropyl-toluenes upon pyrolysis of 3,7,7-trimethyltropilidenes shows that this reaction also occurs thermally and this particular photochemical example was included because of this correspondence.

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CYCLIZATION REACTIONS OF N-HALOAMINES, -AMIDES, AND -IMINES

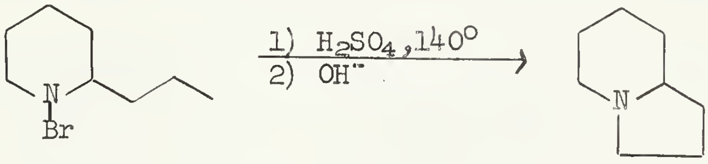
Reported by Daniel R. Bloch March 23, 1967

INTRODUCTION

There have been many reports in the recent literature concerning the use of nitrogen free radicals in organic synthesis.[1] Although cyclization reactions of N-halogenated nitrogen compounds have been known for a long time,[1] only recently has the mechanism,[2-6] the influence of solvent and structure on the efficiency of the process,[1,2,7-9] and addition of nitrogen radicals to unsaturated compounds been studied.[7-13] Preference for formation of pyrrolidines and γ-lactones from the photolysis of N-halo compounds has been well documented.[1-4,8] Readily obtainable starting materials, good yields and relatively simple reaction conditions are characteristic of these reactions.

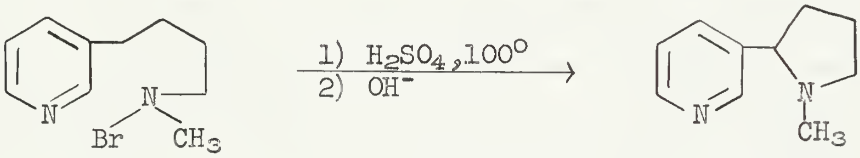
N-HALOAMINES

The first cyclization reaction involving N-haloamines to appear in the literature was reported by Hofmann in 1883.[13] The reaction of N-bromoconiine (I) in hot sulfuric acid and subsequent treatment with base afforded δ-coneceine (II).



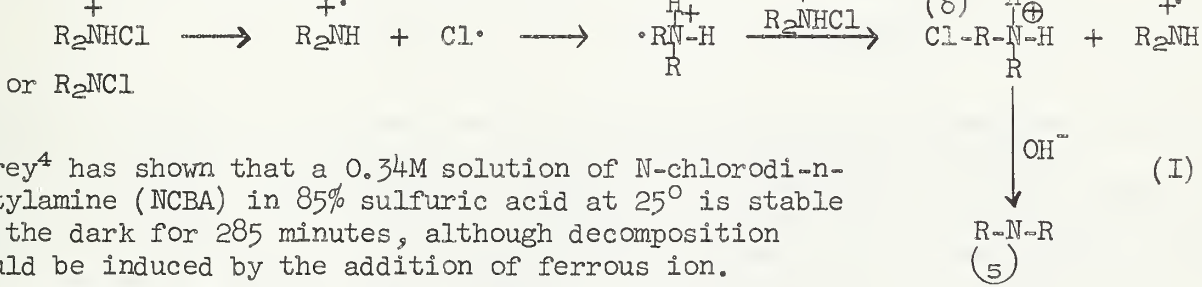
I II

No further work appeared until the early 1900's when Loeffler and co-workers reported further examples of cyclization reactions of N-haloamines including an elegant synthesis of nicotine (III).[14] Thus, reactions of this nature have been called Hofmann-Loeffler (H-L) reactions, although other names have been used.[1] In a review by Wolff,[1] a table of reported H-L reactions has been compiled which is complete through the 1950's and describes reactants, products and reaction conditions.



III

Wawzonek[3,5] was the first to study the mechanism of the H-L reaction and later work by Lukes[6] and Corey[4] have shown the reaction to be a free radical chain process. The following mechanism has been proposed.



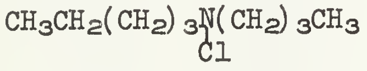
$$\overset{+}{R_2NHCl} \text{ or } R_2NCl \longrightarrow \overset{+\cdot}{R_2NH} + Cl\cdot \longrightarrow \cdot R\overset{H+}{\underset{R}{N}}-H \xrightarrow{\overset{+}{R_2NHCl}} \overset{(\delta)}{Cl-R-}\overset{H\oplus}{\underset{R}{N}}-H + \overset{+\cdot}{R_2NH} \xrightarrow{OH^-} R-N-R \quad (5) \qquad (I)$$

Corey[4] has shown that a 0.34M solution of N-chlorodi-n-butylamine (NCBA) in 85% sulfuric acid at 25° is stable in the dark for 285 minutes, although decomposition could be induced by the addition of ferrous ion. Photolysis of the NCBA solution showed an induction period which could be essentially removed by purging the solution with nitrogen. The reaction could be interrupted by removing the light source and started immediately by irradiating again. These features are characteristic of radical chain reactions.

Corey[4] prepared the N-chloro compounds by passing chlorine gas over a ligroin (60°-90°) solution of the amine. The resulting solution was washed with dilute acid and dilute base before extracting the chloroamine into 85% sulfuric acid. For reactions in anhydrous solvent, the ligroin solution was washed, dried, and concentrated in vacuo. An aliquot of the residue was taken up in absolute acetic acid. The amount of N-chloroamine assumed present was based on the total amount of active chlorine as determined by titration.

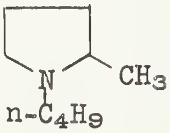
H-L reactions involving acyclic reactants generally lead to pyrrolidines[1,4,8] which are formed (eq 1) by a cyclic mechanism involving the nitrogen and a hydrogen on a δ-carbon. The predominance of hydrogen removal at the δ-carbon favors an intramolecular hydrogen abstraction which occurs preferentially thru a quasi-six-membered transition state. If the process were intermolecular, one would expect more random hydrogen abstraction giving a greater variety of products.

Radicals which abstract hydrogen atoms from carbon generally show a preference for hydrogen in the order tertiary > secondary > primary. This same order of reactivity is followed for H-L reactions. In the free radical decomposition (85% sulfuric acid, 95°) of N-chlorobutylamylamine (IV), two products are possible from hydrogen abstraction at a δ-carbon. 1-n-Butyl-2-methylpyrrolidine (V) would result from secondary hydrogen abstraction and 1-n-amylpyrrolidine (VI) would be formed from primary hydrogen abstraction. The fact that (V) was the only tertiary amine isolated shows the preference of secondary over primary hydrogen abstraction. For a comparison of the reactivity of tertiary and secondary hydrogen and of tertiary and primary hydrogen, the N-chloro derivatives of n-butylisohexylamine and n-amylisohexylamine were prepared and subjected to H-L conditions. No tertiary amine could be isolated although the disappearance of N-chloroamine was very rapid and accompanied by the evolution of hydrogen chloride. It was suggested that the tertiary chloro compound was formed and rapidly solvolyzed in strong sulfuric acid. It was also found that t-butyl chloride liberated hydrogen chloride when shaken with 85% sulfuric acid.

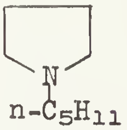


$CH_3CH_2(CH_2)_3N(Cl)(CH_2)_3CH_3$

IV

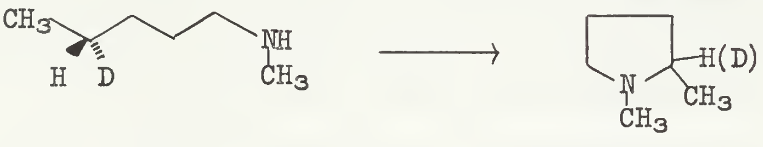


V



VI

The stereochemistry of the H-L reaction was studied by thermally decomposing the N-chloro derivative of (-)-methylamylamine-4-d (VII) in sulfuric acid at 95°. The products, 1,2-dimethylpyrrolidine (VIIIa) and 1,2-dimethylpyrrolidine-2-d (VIIIb), isolated in 43% yield were optically inactive. An isotope effect (k_H/k_D) of 3.54 was observed for the reaction. This result strongly suggests the decomposition involves an intermediate in which the δ-carbon is trigonal.



VII VIIIa,b

As evidence that a δ-chloro compound is an intermediate, Corey[4] treated the solution resulting from photolysis of NCBA with silver ion. Practically no silver chloride precipitated. When the resulting solution was made basic, silver chloride was obtained in ca. 99% yield. Reaction under thermolytic conditions gave a 65% yield of silver chloride. This suggests that the unreactive chlorine was bound to a carbon atom prior to hydrolysis. Since basification resulted in cyclization to the δ-carbon and freeing of the chloride, it is reasonable that the chloride was bound to the δ-carbon. Wawzonek[5] was successful in isolating the 4-chloro derivative in 37% yield from the decomposition of NCBA in sulfuric acid.

Recent work by Neale[8] has shown that side reactions may also be important in the photolytic decomposition of NCBA. He studied the reaction with respect to a) acidity, b) degree of purity of chloroamine, c) applied irradiation and d) the rate at which nitrogen swept the reaction mixture. Most decompositions were run at 20° in acetic acid 1.5M in water while the molarity of sulfuric acid was varied (Table I).

Table I Photolytic Rearrangement of N-Chlorodi-n-butylamine[a]

Entry[b,c]	Molarity[d]		Source[e]	Decomposition[f]	% Yield of N-butylpyrrolidine
	H_2SO_4	Bu_2NCl	Bu_2NCl		
1	0	0.225		2910	0
2	0.5	0.260		62	42
3	1.0	0.255		52	59
4	2.5	0.245		47	80
5	1.5	0.44	U-1	0.81	75
6	1.5	0.46	U-2	1.62	42
7	1.5	0.46	U-1	1.13	41
8	1.9	0.46	U-1	0.96	56
9	3.9	0.46	U-1	0.37	88
10	1.5	0.46	U-2	1.08	—
11	1.9	0.46	U-2	0.98	65
12	3.9	0.46	U-2	0.34	—
13	1.9	0.46	D	0.43	87
14	3.9	0.46	D	0.24	—
15	7.7	0.46	D	0.16	95
16	1.0	0.46	D	0.05	49
17	0.97	0.48	U-1	0.10	17
18	1.0	0.25	U-1	0.22	60
19	2.5	0.24	U-1	0.14	75

[a] Entries 1-4, ref 4; entries 5-19, ref 8. [b] Irradiation: entries 1-4, quartz lamp, range 200-400 mμ; entries 5-19, Hanovia mercury arc lamp with filter, transmition 300-400 mμ. [c] Nitrogen flow: entries 1-4, reaction run under nitrogen; entries 6-19, nitrogen bubbled slowly through solution; entry 5, nitrogen rapidly bubbled through solution. [d] Solvent: entries 1-4, 18 and 19 run in anhydrous acetic acid; entries 5-17 run in acetic acid 1.5M in H_2O. [e] Entries 1-4, prepared as in ref 15. [f] Determined by loss of active chlorine: entries 1-4 are half-life values*; entries 5-19 are in mmoles of chloroamine consumed per min., which is constant for 0-80% of the reaction, except entry 17:0-30% (ref 27).

The chloroamine was prepared from NCS and amine in ether by stirring for one hour, washing with water and dilute sulfuric acid, drying and evaporating the solvent. Reagent grade NCS and amine gave product (U-I), recrystallized NCS and amine gave product (U-II) and distilled U-I gave product (D). Increased chloroamine purity increased yields of N-n-butylpyrrolidine (NBP) and decreased the rate of reaction (Table I).

When the intensity of the irradiation was decreased or lower wave lengths filtered out, the rate of reaction was suppressed and the yields of NBP were decreased. The rate of flow of nitrogen bubbled through the reaction mixture also determined the rate of reaction. Increased rate of flow increased the yield of NBP but decreased the rate of reaction. Trapping spent nitrogen showed volatile substances were being removed from solution by the nitrogen.

In the dark, acid solutions of distilled and undistilled chloroamine were unstable and UV spectra showed formation of a new compound with λ_{max} at 306 mμ. At a given sulfuric acid concentration in acetic acid 1.5M in water, the rate of formation of this new compound in the dark was the same for distilled and undistilled chloroamine. The rate was also found to be dependent on sulfuric acid concentration. In a solution 1M in sulfuric acid decomposition is rapid whereas in a solution 4M in sulfuric decomposition is very slow.[8] The absorbing species was proven to be volatile by

*in min.

sweeping it in a nitrogen stream from a weakly acidic solution of undistilled chloroamine into an acetic acid trap. Extraction with pentane gave a solution with absorption at 307 mμ. The species responsible for this absorption was shown to be N,N-dichloro-n-butylamine by comparison with a sample formed from NCS and butylamine (λ_{max}^{ether} 307, ϵ_{max} 330).

Photolytic decomposition of NCBA was followed by periodically taking the UV spectra of aliquots. When chloroamine of purity U-I and U-II was photolyzed in aqueous acetic acid, new variable absorption appeared in the region 312-320 mμ which grew to a miximum near 60-70% reaction and disappeared when the active titer fell to zero. A less pronounced maximum appeared in the region 320-340 mμ in anhydrous acetic acid. When distilled chloroamine was used the new absorption which appeared (λ_{max} 306 mμ) remained constant. In solutions of excess strong acid (7.7M acid:0.46M chloroamine) no new absorption appeared during reaction. It is apparent that dichloroamine is formed during photolysis of chloroamine solutions although it is unstable under the reaction conditions and does not accumulate in solution. At lower sulfuric acid concentrations, dichlorobutylamine formation may compete favorably with the H-L reaction which could account for decreasing yields of pyrrolidines with decreasing acid concentration (Table I).

Corey found that the rate of decomposition of chloroamine increased with increasing sulfuric acid concentration (Table I, entries 1-4) while Neale stated his results (Table I, entries 8-15) were "in direct contrast" to Corey's and that the rate decreased with increasing acid concentration. Neale also reported that in solutions ca. 0.5M in chloroamine, reactions are quite slow when the molar ratio of sulfuric acid to chloroamine was 1:1 or 2:1 (Table I, entries 16 and 17). At low acid-amine ratios, it appears that both researchers' data indicate an increase in rate with an increase in sulfuric acid concentration. Neale's values support this conclusion up to an acid-chloroamine ratio of 3:1.

Although the mechanism of the H-L reaction is generally agreed upon, the initiating species is subject to controversy. Wawzonek proposed that the protonated N-chloroamine is the initiating species since the chloroamine exists mostly in the protonated form in sulfuric acid solutions. Corey[4] suggested that unprotonated N-chloroamine is the initiator. Protonated NCBA shows no appreciable absorption above 225 mμ, whereas free amine absorbs at higher wave length (λ_{max}^{HOAc}267, ϵ_{max} 320)[17] (Fig I).

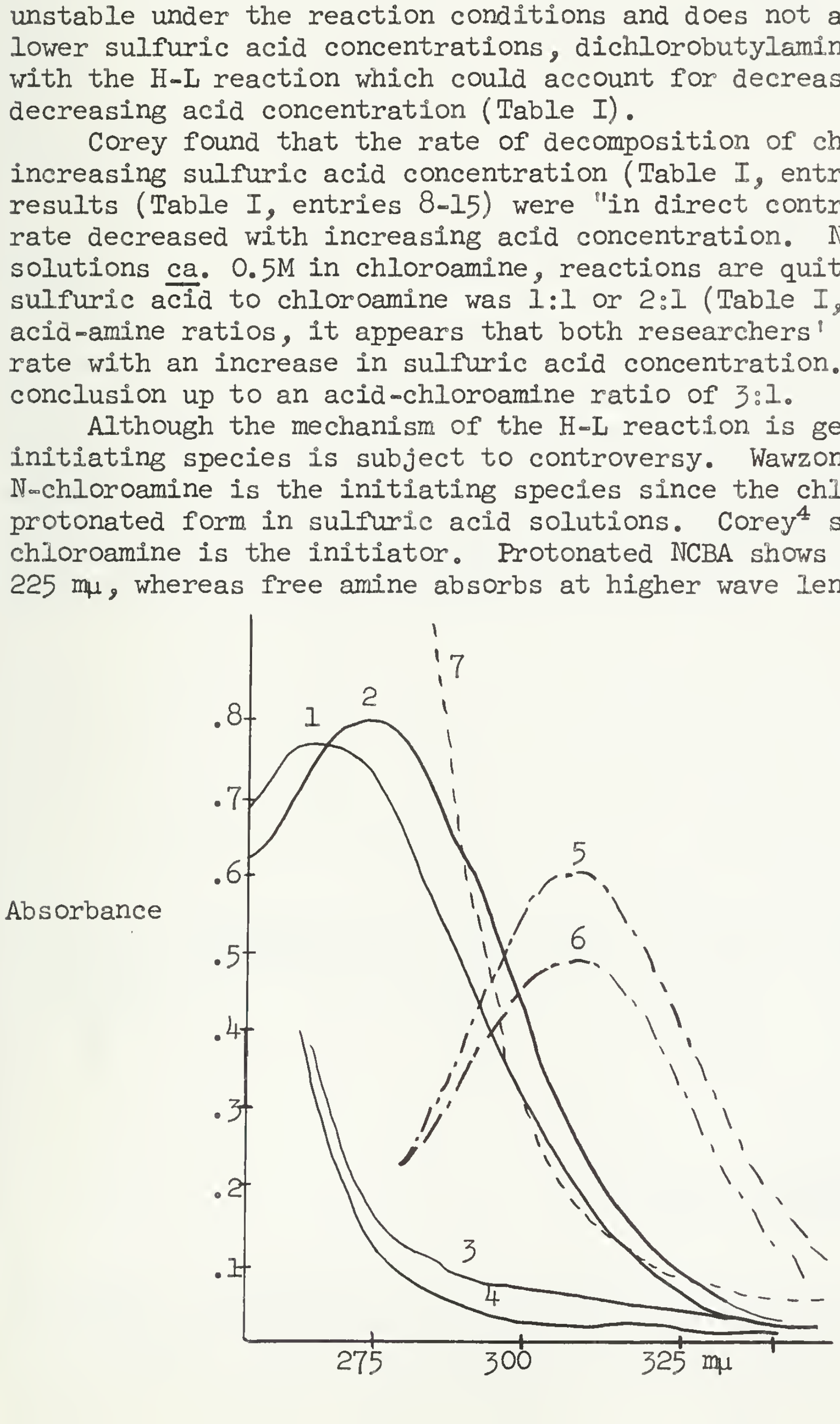


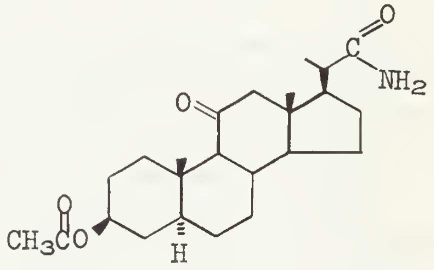
Fig I. N-chlorodi-n-butylamine: (1) 2.65 x 10^{-3}M in HOAc, cell 1.0 cm; (2) 1.98 x 10^{-3}M in CCl_4, cell 1.0 cm; (3) 0.46M in H_2SO_4-1.5M H_2O-HOAc; cell 0.105 cm; (4) 0.46M in 1.5M H_2SO_4-1.5M H_2O-HOAc, cell 0.105 cm. N,N-Dichloro-n-butylamine: (5) 1.86 x 10^{-3}M in ether, cell 1.0 cm, from NCS and butylamine; (6) 1.56 x 10^{-3}M in pentane, cell 1.0 cm, isolated from reaction mixture; (7) absorbance of 2 mm. thickness Pyrex glass vrs. air.

Corey's data show that the rate of reaction increases with increasing sulfuric acid concentration. If free chloroamine is the initiating species, its concentration should decrease with increasing acidity and, hence, decrease the initiation rate. Thus acid catalysis must involve acceleration of the propagation process and/or retardation of chain termination. It seemed likely to Corey that strong acid should inhibit chain termination. The interaction of two protonated, positively charged radicals by coupling or atom transfer would be slower than for neutral species, especially if the ions were solvated. The photolytic decomposition of NCBA in carbon tetrachloride[18] and anhydrous acetic acid,[2,4] where amine is unprotonated, is very slow relative to the acid catalyzed reaction (Table I, entry 1). There are at least three possible explanations why the reaction is slow: a) Neale's suggestion that the unprotonated chloroamine is a poor initiator, b) Corey's proposal that chain termination is more favorable for unprotonated nitrogen radicals, and c) an acid catalyzed propagation sequence which has not yet been defined.

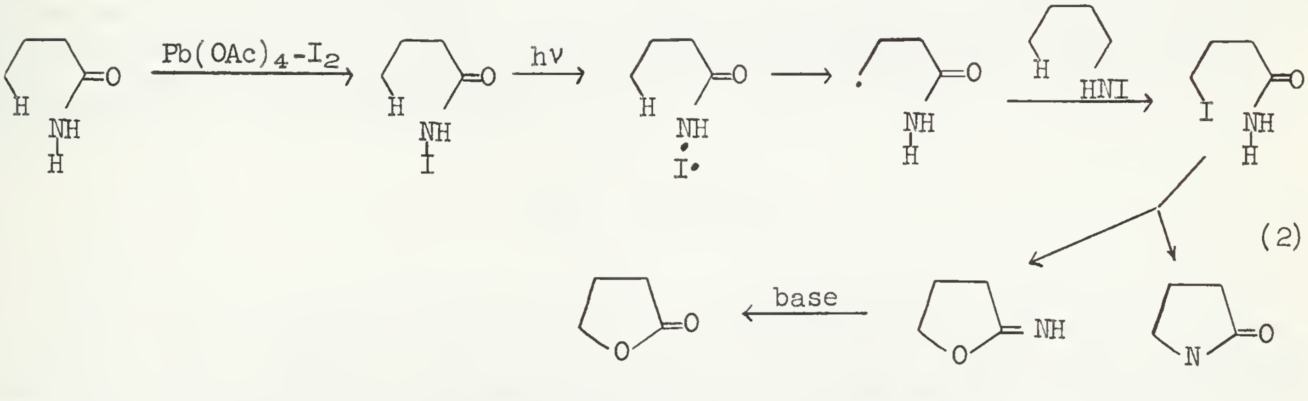
Neale[8] suggested that the N,N-dichloro-n-butylamine is the initiating species in the H-L reaction, since it is formed and decomposed during photolysis (λ_{max} 306, ϵ 320). He further argued that if free N-chloroamine were the initiating species, its low concentration and extinction coefficient would require it to absorb light and dissociate very efficiently (Fig I).

N-HALOAMIDES AND N-HALOIMIDES

The mechanism proposed for the photolytic decomposition of N-haloamides and N-haloimides is analogous to that proposed for the H-L reaction (eq 1).[11,19,20] These reactions are initiated by light and peroxides and are inhibited by bubbling oxygen through the reaction solution. One notable exception is that, in general, acid is not needed to catalyze the reaction. Although reaction conditions vary, hydrogen abstraction at the γ-carbon is predominant, with subsequent formation of γ-lactones. Barton[19] has done the most extensive mechanistic study to date. In a search for a general method of forming saturated lactones from saturated acids, photolysis of N-iodoamides afforded γ-iminolactones which could be hydrolyzed to γ-lactones. Iodination of 3β-acetoxy-11-oxo-5α-pregnane-20-carboxamide (IX) with lead tetraacetate and iodine in benzene gave ca. 55% yield of lactone upon alkaline hydrolysis. In a similar manner, orthotoluamide gave phthalide and stearamide gave γ-stearolactone. The following mechanism was proposed:

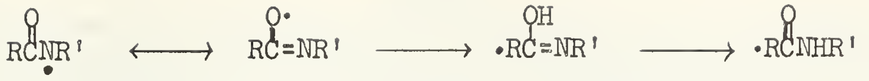


IX



(2)

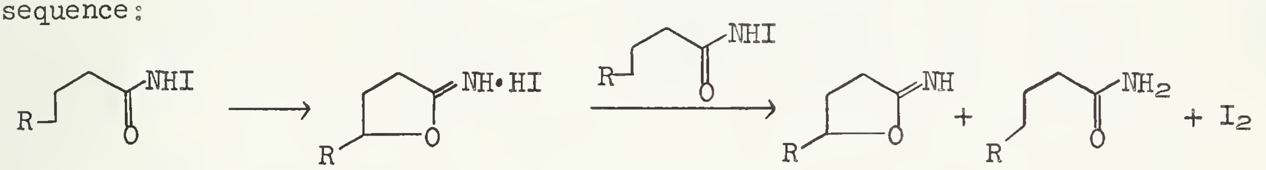
Of course, one cannot rule out the possibility in any of the known N-haloamide or N-haloimide rearrangements that intramolecular hydrogen abstraction is performed by amide oxygen rather than nitrogen, followed by tautomeric regeneration of the normal amide group (eq 3). This would involve the same size cyclic transition state as preferred by alkoxy radicals in the light induced radical chain decomposition of



$$R\overset{O}{\overset{\|}{C}}\underset{\bullet}{N}R' \longleftrightarrow R\overset{O\cdot}{C}{=}NR' \longrightarrow \cdot R\overset{OH}{C}{=}NR' \longrightarrow \cdot R\overset{O}{\overset{\|}{C}}NHR' \qquad (3)$$

t-butylhypochlorites with side chains of three carbons or longer. These reactions occur largely via an intramolecular path (1,5 hydrogen shift) to give δ-chloroalcohols.[24] An intermediate N-iodoamide was isolated by reacting lead tetraacetate and iodine with benzamide. N-Iodoamides could also be prepared by reacting amides with t-butylhypochlorite and iodine in various solvents where the iodinating species was shown to be t-butylhypoiodite.[19] Crystalline N-iodo compounds were obtained from benzamide, succinimide, n-butyramide, n-hexanamide and n-octadecanamide using hypohalite as the iodinating agent. N-Iodo-n-octadecanamide was isolated in two forms with melting points of 114° and 120°. Whether these were two crystal forms or two geometrical isomers has not been determined.

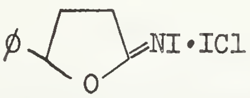
Solutions resulting from photolysis of N-iodoamides showed a strong infrared band at 1680 cm^{-1}. This suggested the presence of an amide or iminolactone. Washing these solutions with sodium hydrogen sulfite caused the appearance of a γ-lactone band in the infrared spectrum. The following results were obtained in order to determine which of the two species was present after photolysis and before hydrolysis. γ-Iodobutyramide was found to be unstable at room temperature in a "humid" atmosphere and cyclized spontaneously to give γ-lactone. Photolysis of the higher melting N-iodo-n-octadecanamide showed that all the iodine originally present as N-iodo was found as molecular iodine at the end of the reaction. Yields were never greater than 50% unless excess iodinating agent was used. These results suggested the following sequence:



(4)

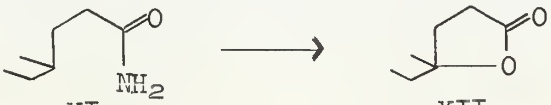
During the initial period of darkness there was no appearance of iodine. Irradiation caused a rapid development of iodine. During a further period of darkness only a small amount of iodine appeared which was about 10% of the amount of iodine liberated during the light period. Further periods of light and darkness produced the same effects.

The solution resulting from photolysis of N-iodo-n-octadecanamide was divided into two equal portions. One portion was hydrolyzed in the normal manner while the other was treated with zinc dust and acetic acid before hydrolysis. Both solutions gave the same yield of lactone upon hydrolysis. It has been shown[19] that γ-iodobutyramide is smoothly converted to butyramide under identical treatment with zinc and acetic acid. These results suggest that iminolactone is responsible for the infrared band at 1680 cm^{-1}. Isolation of a derivative of the postulated iminolactone was finally achieved during the photolysis of γ-phenylbutyramide in the presence of an excess of t-butyl hypochlorite and iodine. The crystalline compound which formed during the photolysis was regarded as the iodine chloride complex (X) of N-iodo-γ-phenylbutyroiminolactone. Excess iodinating agent reacting with γ-iminolactone could be responsible for the formation of X. Infrared, NMR, and microanalytical data support the structure assigned to (X).



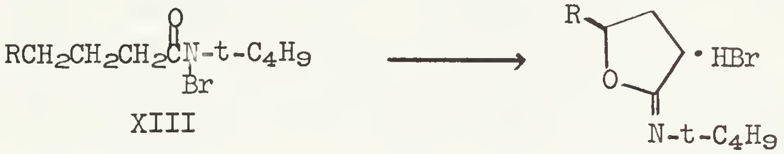
X

Like the H-L reaction, optically active compounds with an asymmetric γ-carbon rearrange to give racemic product. Photolysis of optically active (+)-4-methylhexanamide (XI) in the presence of t-butylhypochlorite and iodine gave racemic 4-methyl-4-hexanolactone (XII). An insertion mechanism was thus excluded.



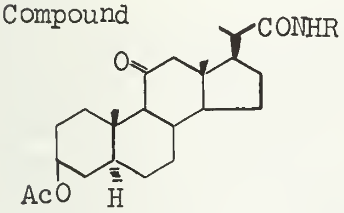
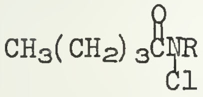
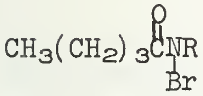
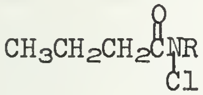
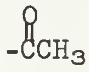
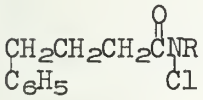
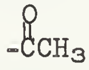
XI XII

N-Bromoamides and N-chloroamides can also be photolytically rearranged to give γ-lactones. Rearrangement is most efficient with N-t-butyl derivatives of the amides. Treatment of a N-t-butylamide with 10% excess t-butylhypobromite in carbon tetrachloride at room temperature gave the N-bromo compound. On subsequent irradiation, active bromine was lost within ten minutes. The infrared spectra of the resulting solution showed a strong absorption characteristic of secondary amides. Brief heating afforded the iminolactone (eq 5) which could be precipitated by dilution with anhydrous ether. The N-chloroamides could not be rearranged as readily as their N-bromo counterparts. Heating the γ-chloro compound in sulfuric acid was required for ring closure. Table II lists reaction conditions for photolytic rearrangement of N-iodo-, N-bromo-, and N-chloroamides.



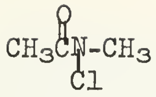
XIII (5)

Table II. Photolytic Rearrangement of N-Haloamides and N-Haloimides

Compound	R Substituent	Solvent	Temp °C	Light Source	Time, min	% γ-Lactone
	$-H$	benzene	15	a	300	46.8
	$-CH_3$	$HCCl_3$	reflux	b	90	None
	$-C_6H_5$	$HCCl_3$	reflux	b	240	17.2
 $CH_3(CH_2)_3\overset{O}{\overset{\|}{C}}\underset{Cl}{N}R$	$-H$	benzene	24	c	120	37
	$-t-C_4H_9$	benzene	26	c	10	71
		CCl_4	26	c	10	79
	$-C(C_6H_5)_3$	benzene	25	c	10	None
	$-CH_3$	benzene	25	c	150	None
		CCl_4	25	c	150	None
	$-C_6H_5$	benzene	25	c	120	None
 $CH_3(CH_2)_3\overset{O}{\overset{\|}{C}}\underset{Br}{N}R$	$-CH_3$	benzene	30	c	20	43
	$-t-C_4H_9$	benzene	23	c	25	53
 $CH_3CH_2CH_2\overset{O}{\overset{\|}{C}}\underset{Cl}{N}R$	$-H$	$CFCl_3$	0	d	18 hrs	3
	 $-\overset{O}{\overset{\|}{C}}CH_3$	$CFCl_3$	0	d	8-9 hrs	17
 $\underset{C_6H_5}{CH_2}CH_2CH_2\overset{O}{\overset{\|}{C}}\underset{Cl}{N}R$	$-H$	$CFCl_3$	25	d	8 hrs	19
	 $-\overset{O}{\overset{\|}{C}}CH_3$	$CFCl_3$	0	d	11 hrs	37

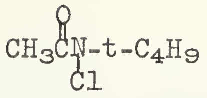
[a]125-watt high-pressure mercury arc lamp, [b]tungsten lamp, [c]Hanovia 100-watt medium pressure mercury arc lamp, and [d]Rayonet 3500 A° lamp augmented by a Victor 500-watt mercury vapor lamp.

The lower yields for N-methyl compounds (Table II) could be attributed to dehydrohalogenation resulting from loss of hydrogen α to nitrogen (N-C-H). Irradiated N-chloro-N-methylacetamide (XIV) reacted completely within 30 minutes while N-t-butyl-N-chloroacetamide (XV) was unreactive for 180 minutes under identical conditions (benzene, Pyrex). Attempts to cyclize N-trityl and N-phenyl derivatives of



$CH_3\overset{O}{\overset{\|}{C}}\underset{Cl}{N}\text{-}CH_3$

XIV

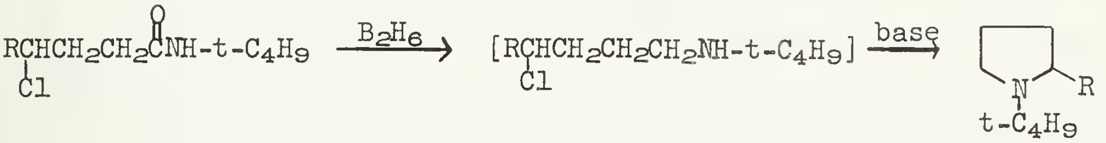


$CH_3\overset{O}{\overset{\|}{C}}\underset{Cl}{N}\text{-t-}C_4H_9$

XV

pentanoamide, which in common with the N-t-butylamides lack α hydrogens, were unsuccessful. While N-bromo compounds could be rearranged in benzene or carbon tetrachloride, N-chloro rearrangements were successful only in benzene and pyridine. This solvent effect is presently being investigated.[25,26]

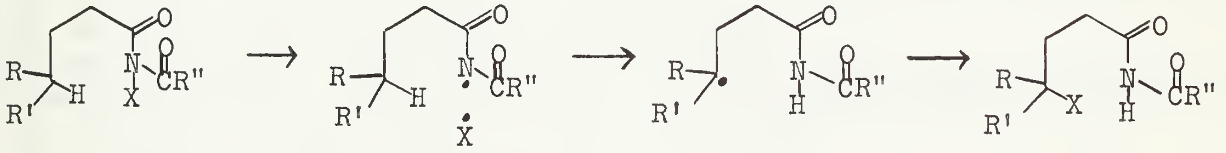
The rearrangement products of N-chloro-N-t-butylpentanoamide and N-chloro-N-t-butylhexanoamide were reduced to the 4-chloroamines with diborane. Refluxing for three hours gave the corresponding pyrrolidine (eq 6). This is another way of



(6)

preparing H-L rearrangement products without using strong acids.

The hydrogen abstracting, chain-carrying species in aliphatic,[22] allylic and benzylic[23] halogenations by N-halosuccinimides is normally the halogen atom, rather than the succinimidyl radical. Since intramolecular rearrangements are generally more rapid than the corresponding intermolecular reactions, it is possible that acyclic imidyl radicals might rearrange at rates fast enough to permit selective introduction of functional groups at the γ-position of imides (eq 7).[20]



(7)

XVI

Petterson has shown that γ-chloro-N-acetylamides (XVI, X=Cl, $R''=\overset{O}{\overset{\|}{C}}CH_3$) are formed from compounds having primary, secondary, or benzylic γ-hydrogen. N-Chloroimides were readily made (> 90%) by reacting the parent imide with t-butylhypochlorite in methanol.[24] Photolysis under helium produced 4-chloro derivatives which were converted to lactones by acid hydrolysis. Table II shows that under similar conditions N-acetylamides give better yields of γ-lactone than do the corresponding N-hydroamides. The reason why the second carbonyl group on nitrogen promotes rearrangement is not yet known. One might expect from Neale's work that benzene would be a better solvent for imide rearrangements. Preliminary studies show that reaction times in benzene are decreased but yields are also diminished.[28]

CONCLUSION

Respectable yields from N-halo cyclization reactions and the short series of operations involved in the reaction further spotlights the increasing usefulness of nitrogen radicals in organic synthesis. These reactions serve as an example of a free radical synthesis which may be difficult or even impossible by a nonradical approach. The mechanism of these reactions is generally agreed upon, although the species responsible for initiating the reactions must be subject to further investigation. Rearrangement conditions and yields are dependent upon the solvent, groups substituted on nitrogen in amides and the substituents at the δ-carbon (amines) or γ-carbon (amides and imides).

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THE THERMAL ENDO-EXO ISOMERIZATION OF SOME DIELS-ALDER ADDUCTS

Reported by Tommy L. Chaffin April 6, 1967

According to the Alder Rule[1] of Diels-Alder additions, of the two stereoisomeric adducts of a cyclic diene with a dienophile, that one which is formed with the maximum accumulation of double bonds will preponderate. Although there are many exceptions to this rule, there has been controversy as to whether they result from the isomerization of the initially formed endo adduct directly to to the exo:

$$\text{Addends} \rightleftharpoons \text{Endo} \rightleftharpoons \text{Exo}$$

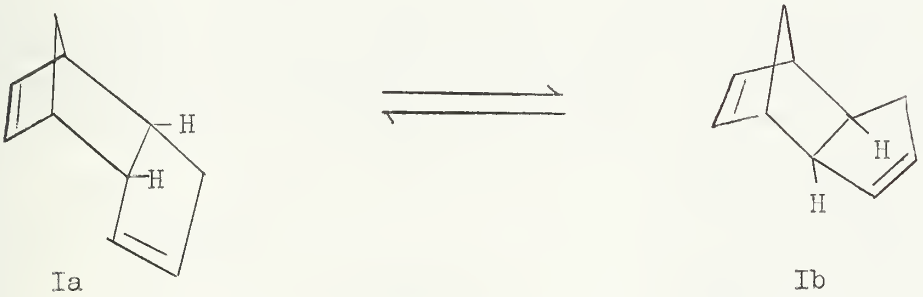
or whether the endo product is reversibly formed from the addends which can slowly form the thermodynamically more stable exo isomer:

$$\text{Endo} \rightleftharpoons \text{Addends} \rightleftharpoons \text{Exo}$$

Any type of direct isomerization which does not involve dissociation into kinetically free addends will be termed an "internal" mechanism in contrast to an "external" mechanism such as dissociation and recombination. This seminar will present the evidence for these two possibilities.

ORIGIN OF THE PROBLEM

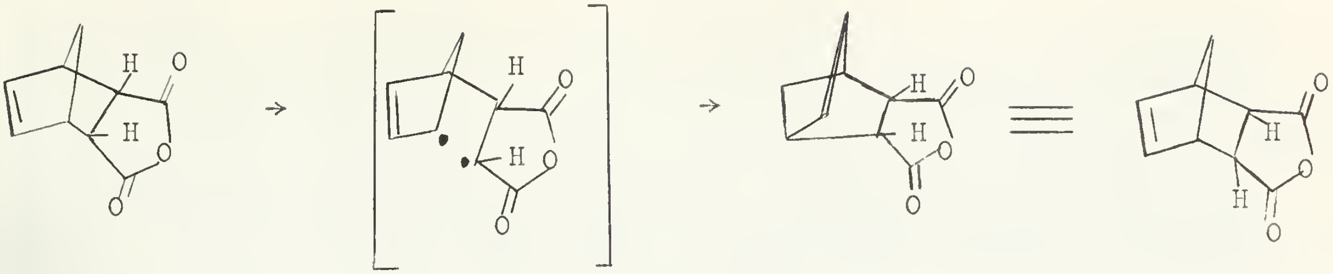
The first thermal isomerization of this type was reported in 1933 by Alder and Stein[2]. They observed the isomerization of endo-dicyclopentadiene (Ia) to exo-dicyclopentadiene (Ib) at 170°. They felt that this was due to the existence



of an equilibrium with a small concentration of the monomer under the reaction conditions.

It has also been observed[1,3] that addition of maleic anhydride to 6,6-pentamethylenefulvene at room temperature produces the endo isomer while at higher temperatures mixtures of the isomeric adducts are found. This, too, was explained on the basis of the reversible formation of small concentrations of the addends. Woodward noted[3] that the dihydro derivatives did not isomerize and that a solution of the adducts in benzene or ethyl acetate turned yellow when warmed, presumably from the colored fulvene. The exo isomer was considerably more stable and therefore the reaction was thought to be kinetically controlled at low temperatures. This dissociation-recombination mechanism has been proposed[4] to be a general one for Diels-Alder adducts of cyclic dienes.

Craig, in 1951, reported[5] that heating the endo adduct of maleic anhydride and cyclopentadiene (IIa) to 190° produced the exo isomer (IIb) and not the addends as had been previously reported.[6] He concluded that the isomerization proceeded by means of a non-isolable intermediate and noting that the dibromo compound did not rearrange, he proposed the following mechanism involving the double bond:



IIa

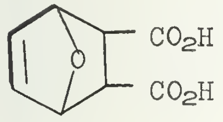
IIIb

This mechanism can explain why the addends were observed for the rearrangement of the fulvene-maleic anhydride adducts, since this type of mechanism would be impossible for fulvene.[7]

Schroder has proposed[8,9] that the endo-exo isomerization of dicyclopentadiene is an intramolecular rearrangement.

EXPERIMENTAL EVIDENCE

Berson has studied[10] the rate of formation of the endo and exo adducts (III) from furan and maleic acid. Contrary to a previous report[11], the reaction does not produce only the endo isomer. Since the adducts are quite unstable[12] they were isolated by saturating the double bond with bromine to prevent retrogression. If both isomers are formed directly from the addends, then the rates of formation of both should be at their maxima when the concentration of the addends is highest, at the beginning. This is assuming second-order kinetics for both isomers. On the other hand, if the exo isomer is formed directly from the endo without forming the kinetically free addends, then the endo isomer would have its maximum rate of formation at the beginning and the exo isomer should have its maximum rate at some later time corresponding to the maximum concentration of the endo isomer. The data are shown graphically in Figure 1, and although it seems to support the direct isomerization, the analytical method could not be tested on mixtures of known composition due to the instability of the endo adduct, and the authors chose not to distinguish between the proposed mechanistic paths.



III

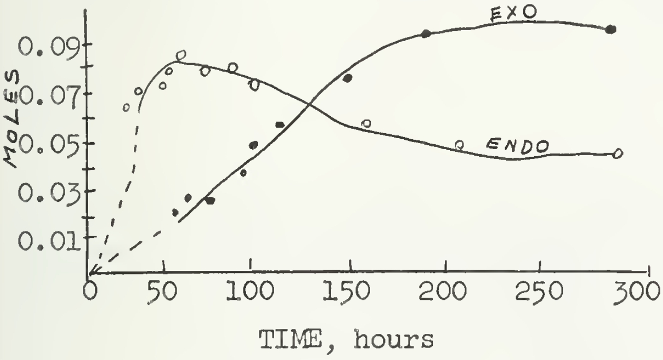


Figure 1

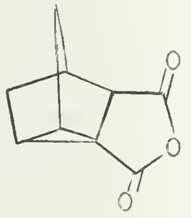
It has been reported[5] that the adduct of cyclopentadiene and maleic anhydride (II) undergoes diene interchange at 200° with 2,3-dimethylbutadiene and dienophile interchange with fumaric acid. This would seem to indicate that at least part of the rearranged product results from retrogression.

Berson[13,14] studied the isomerization of the endo adduct of maleic anhydride and cyclopentadiene (II) with C^{14} labeled carbonyl groups in the presence of an equimolar amount of unlabeled maleic anhydride in boiling decalin (188.5°). Since the endo adduct exchanged rather rapidly under the reaction conditions, it was necessary to determine the activity of the formed exo adduct at short reaction times. This, in turn, meant that small amounts of the exo adduct were formed. Therefore the amount and activity of formed exo adduct were determined by isotopic dilution. If the isomerization proceeds by purely an internal or direct isomerization, the activity of the exo adduct formed at any time will be the same as the endo activity at that time. If the isomerization proceeds by an external path, that is, by retrogression, then the activity of the exo adduct formed at any time will be the same as the activity of maleic anhydride

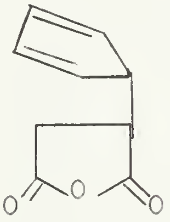
at that time. By dividing the reaction into arbitrarily small time increments the theoretical activity to be expected of the exo adduct by each path was calculated by graphical integration. The activity of the exo adduct isolated was considerably higher than that expected by a purely external path and therefore it was concluded that a significant part of the isomerization occurred by a direct path not involving kinetically free fragments. They felt that the most likely mechanism involved cage recombination or some intermediate complex of the addends. It has since been demonstrated[15] that the rate of addition of cyclopentadiene and maleic anhydride is too slow to compete with diffusion and therefore cage recombination is not a reasonable possibility.

Baldwin and Roberts[16] conducted the isomerization of the endo isomer in the presence of tetracyanoethylene (TCNE) which had been reported to be a very good dienophile[15]. The assumption was that TCNE would react with cyclopentadiene much faster than would maleic anhydride. Only partial inhibitiion of the formation of the exo isomer was observed which was taken to indicate that an internal and an external mechanism were in competition.

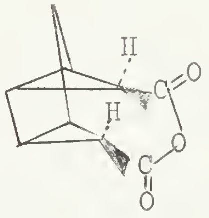
A number of possible internal mechanisms have been proposed in addition to the 7,5-hydrogen shift suggested by Craig[5]. They fall basically into two categories: mechanisms in which both diene-dienophile bonds are broken with the fragments contained in a solvent cage or as a complex; and mechanisms in which any other bonds are broken. In the second category are included: (1) an acid catalyzed Wagner-Meerwein rearrangement[17]; (2) a base catalyzed inversion (enolization)[18]; (3) formation of a nortricyclyl derivative (IV) or cyclopentadienyl succinic anhydride (V)[5,19,20]; (4) and cleavage of the 2,3-carbon-carbon bond to form a common intermediate- possibly a double cyclopropane structure (VI)[15].



IV



V

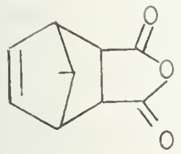


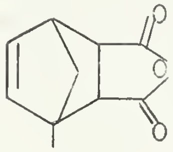
VI

It has been observed that the rearrangement is not catalyzed by acids or bases[5] which would seem to eliminate the first two proposals. Roberts and co-workers[21] planned to study the internal mechanism further by rearranging the endo adduct which was stereospecifically labeled in only one carbonyl. They planned to use TCNE as a scavenger for cyclopentadiene so that all of the exo isomer formed would result from the internal mechanism. It was hoped that the position of the label in the exo isomer would eliminate some of the possible internal mechanisms. However, it was found that maleic anhydride reacts with cyclopentadiene at a rate comparable to that of TCNE under the reaction conditions. An alternative would be to run the reaction in an excess of maleic anhydride so that essentially all of the exo product formed by the internal process would be labeled and none of that by the external process. First, however, the isomerization was carried out again on the adduct with uniformly labeled carbonyls[22] to re-examine the case for the internal mechanism. This was prompted by the fact that TCNE was found not to be an effective diene scavenger for this case and by the observation that in Berson's exchange experiment[14] in boiling decalin not all of the maleic anhydride was in solution. Furthermore, a considerable amount of the maleic anhydride sublimes out of the reaction within a few minutes. Both of these experiments, then, prejudice the results toward an internal process. When essentially the same experiment was run with an equimolar amount of the labeled endo isomer and unlabeled maleic anhydride in t-pentylbenzene, which gave a homogeneous solution, the results indicated that no internal mechanism was involved in the

isomerization.

In other work, Miranov has shown[23] that isomerization of the 7-methyl (VII), 1-methyl (VIII), and 6-methyl (IX)-5-norbornene-2,3-endo-cis-dicarboxylic anhydrides gives a 2:1 ration of 1- to 6-methyl adducts and only a trace of the 7-methyl adduct. Even though the endo-exo ratio was not determined this is interpreted solely in terms of dissociation to the addends since substituted cyclopentadienes have been shown to undergo double bond migration under these conditions[24]. Also the endo adduct of maleic anhydride and 1,4-diphenylcyclopentadiene (X) has been reported[25] to give a 1:5 ratio of the exo isomer and 1,5-diphenyl-5-norbornene-endo-cis-2,3-dicarboxylic anhydride (XI). Although the author postulated that the products resulted from two competing mechanisms, it appears that they can be explained in the same way as those of Miranov.


VII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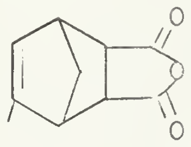
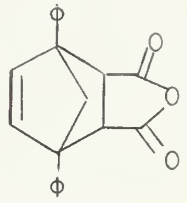
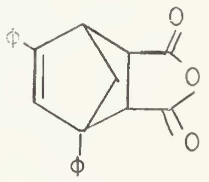

IX



X



XI

Baldwin[26] has studied the isomerization of specifically deuterated dicyclopentadienes (I). An external mechanism should produce scrambling of the deuterium. Statistically, one would expect 25% unlabeled, 25% doubly deuterated and 50% monodeuterated product from monodeuterated starting material. An internal mechanism would preduct all monodeuterated product. This will obviously be complicated by reversible formation of the monomer from one or both of the isomers since the reaction conditions are essentially those used to generate the monomer from the dimer[27]. Therefore if any labeling specificity is found in the product it can be taken as evidence for an internal mechanism, but scrambling of the label could be interpreted as evidence against an internal mechanism only if it can be demonstrated that the specifically deuterated product does not equilibrate under the reaction conditions and that the starting material has not equilibrated before reaction. A specifically deuterated exo dimer was recovered after 90 minutes at 196° during which time no scrambling had occurred. The endo dimer appears to have undergone about 60% equilibration at the end of 7 minutes under the reaction conditions. The results of the isomerization of the endo dimer are shown in Table I.

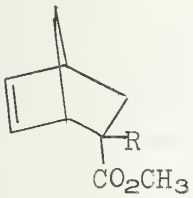
Table I
Deuterium Distributions in Dicyclopentadienes upon endo to exo Rearrangement at 196°

Time, min.	Rearrangement, %	endo Dimer				exo Dimer			
		d_0	d_1	d_2	d_3	d_0	d_1	d_2	d_3
0	0	6	80	4	10				
7	1.1	26	57	16	1	30	47	19	4
60	11	34	42	18	5	28	49	22	2
90	16	67	20	9	3	31	47	21	1

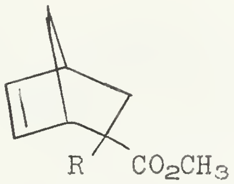
The theoretical distribution of deuterium in the product was calculated on the assumption that both the doubly and the triply deuterated endo starting material had the deuterium in one cyclopentadiene unit. This leads to a calculated distribution of 29.4% d_0, 44.4% d_1, 19% d_2, and 7% d_3. This is in good agreement with the experimental results, and for short reaction times, where

equilibration is incomplete in the starting material, would seem to suggest little if any contribution from an internal mechanism. Herndon and co-workers[30] have arrived at the same conclusions from a kinetic study of the thermal decomposition of the dimers in the gas phase.

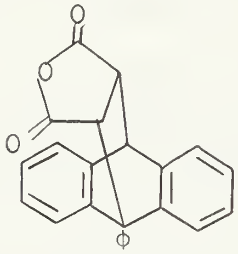
Berson studied the isomerization of optically active adducts of cyclopentadiene with methyl acrylate and methyl methacrylate[19,28]. Heating the optically active exo adduct of cyclopentadiene and methyl methacrylate(XIIb) at 170° in decalin for 3.5 hours gave 5.6% conversion to the racemic endo adduct (XIIa). The recovered starting material was only 7% racemized and it was shown that the optically active endo isomer does not racemize under the reaction conditions. Furthermore, the extent of conversion corresponds to that anticipated on the assumption that the addends are common intermediates for the racemization of the exo isomer and its conversion to endo. Under these circumstances the percent conversion should have proceeded to an extent equal to the percent racemization of exo times the kinetic ratio($\frac{k_{endo}}{k_{exo}}$) for formation of adducts from addends.



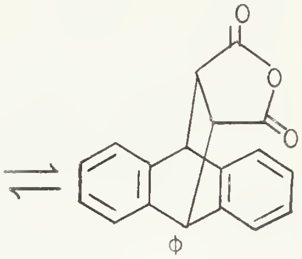
XIIa; R=CH_3
XIIIa; R=H



XIIb; R=CH_3
XIIIb; R=H



XIVa



XIVb

Similar results were also found for the isomerization of the optically active endo adduct of cyclopentadiene and methyl acrylate(XIII). These results strongly indicate the lack of an appreciable contribution from an internal mechanism in this case.

In the systems considered thus far the isomers have been chemically different and it has been necessary to follow the behavior of both species, however for the optically active adduct of 9-phenylanthracene and maleic anhydride (XIV) this is not the case since the isomers are also enantiomers[15]. If an internal mechanism exists which allows interconversion of the enantiomers, loss of optical activity should exceed dissociation into kinetically free fragments. If, however, the rate of loss of optical activity is exactly the same as the rate of dissociation, then there can be no other significant path for racemization. The loss of optical activity of the adduct was followed as a function of time and the first order rate constants determined at three different temperatures. The rates of dissociation were determined spectrophotometrically by means of the diene ultraviolet absorption and found to be identical with those for loss of optical activity.

One final example of this isomerization has been studied[29]. When either the endo or exo adduct of cyclopentadiene and 1,4-benzoquinone-2,3-epoxide is heated to 220° for 10 minutes the resulting mixture consists of an approximately equal mixture of the two isomers as evidenced by a comparison of the infrared spectra with those of known mixtures. When either isomer is heated under the same conditions in the presence of an equimolar amount of TCNE only 1,4-benzoquinone-2,3-epoxide, 2,2,3,3-tetracyano-5-norbornene, and starting material are produced.

CONCLUSION

In the light of these studies there seems to be no firm evidence for any mechanism for the thermal endo-exo isomerization of Diels-Alder aducts other than dissociation and recombination.

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REACTIONS OF NH RADICALS

Terry G. Burlingame April 10, 1967

INTRODUCTION

Imidogen, or NH, may be considered the simplest of the nitrenes; i.e., that class of reactive species containing monovalent nitrogen, which therefore contains six electrons in its outer shell. Several reviews on nitrene intermediates, R-N, in general, have appeared in the literature.[1,2] Imidogen is isoelectronic with the much-studied reactive species carbene, or CH_2.[3] Both of these may exist either as the triplet or as the singlet species (in which case carbon and nitrogen are quite electrophilic due to their electron deficient structure). The most commonly used method to generate NH is through the photodecomposition of hydrazoic acid, HN_3, in which the well-established primary process is as follows:

$$H-N-N\equiv N \xrightarrow{h\nu} NH + N_2$$

Free NH was first detected in 1892.[4] Since that time, the species has been well characterized spectroscopically in the gas phase[5] (by absorption and emission) and in solid matrices at low temperatures[6] (by UV and IR absorption). Less definitive evidence has been obtained for existence of NH in the liquid phase.

The electronic states of NH have been determined spectroscopically.[7]

Ground state: triplet, $^3\Sigma^-$
Lowest excited state: singlet, $^1\Delta$
Second excited state: singlet, $^1\Sigma^+$

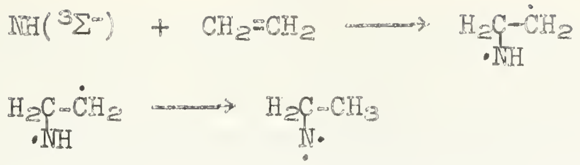
The exact energy separation of these states is not known, although the $^3\Sigma^-$ and $^1\Delta$ levels have been estimated to differ in energy by 27 kcal.[7]

SCOPE

The purpose of this seminar will be to discuss in some detail the gas, solid, and liquid phase reactions of NH radicals with other molecules; to examine the mechanisms proposed for those reactions in which NH is postulated as an important intermediate, and to discuss the validity of such mechanisms in the light of the experimental evidence presented.

REACTIONS OF NH IN THE VAPOR PHASE

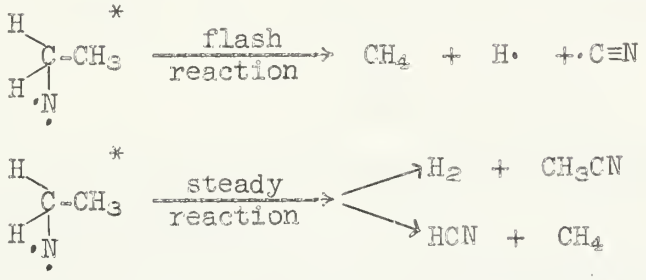
The most systematic analysis to date of the reactions of NH radicals with various organic molecules in the gas phase has been carried out by Lwowski and co-workers.[8] Reactions of methane, ethane, ethylene, butene-1, heptene-3, and 2,3 dimethylbutene-2 with NH radicals generated by the photodecomposition of hydrazoic acid, HN_3, were studied. Two sets of experiments were performed: those in which NH was generated by high energy flash photolysis of HN_3- hydrocarbon mixtures, and those in which steady, slow irradiation of the mixtures was carried out. Flash kinetic spectroscopy performed at various time intervals after irradiation in the flash experiments gave absorption bands ($A^3\pi \leftarrow X^3\Sigma^-$) due to the triplet ground state of the NH radical and bands from highly vibrationally excited $\cdot C\equiv N$ radicals. The C_2 and CH transients were detected in the ethane and ethylene reactions; CH was also detected in the methane reaction. There is a close correlation between the decay time of the NH absorption and the appearance time of the $\cdot C\equiv N$ spectrum. No bands due to singlet NH were observed. The principal nitrogen-containing products in all the flash-initiated reactions were N_2 and HCN. No alkyl cyanides were detected. The slow photolyses yielded in general HCN, alkyl cyanides, saturated hydrocarbons and hydrogen in the gas phase. No analyses for NH_3 or NH_4N_3, almost certainly products of secondary NH reactions, were made. For example, in the case of ethylene-HN_3 mixtures, products obtained were HCN, CH_3CN, CH_4, H_2 and an amorphous solid. The HCN/CH_3CN ratio of .9 was independent of ethylene pressure in the range 80-560 mm. Photolysis of a 0.5:1 mole ratio mixture of DN_3 and HN_3 gave CH_2DCN and CH_3CN in a ratio of 0.25. The following scheme was proposed in view of the above results to occur in both the flash and slow reactions:



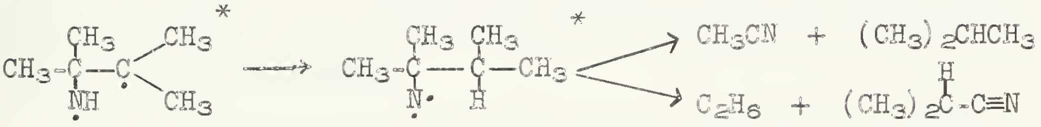
$$NH(^3\Sigma^-) + CH_2{=}CH_2 \longrightarrow H_2\underset{\cdot NH}{C}{-}\dot{C}H_2$$

$$H_2\underset{\cdot NH}{C}{-}\dot{C}H_2 \longrightarrow H_2\underset{\dot{N}\cdot}{C}{-}CH_3$$

Further fragmentation of the nitrene intermediate then occurred according to its energy content:



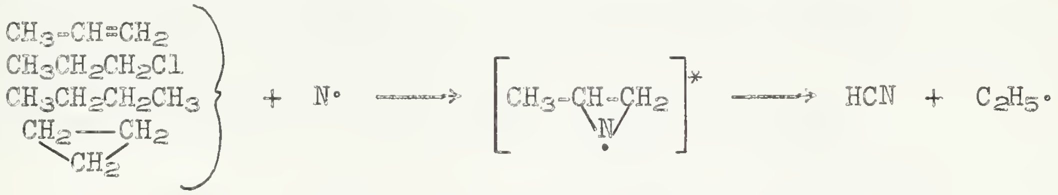
If the above scheme is reasonable, one should expect to find CH_3CN but no HCN in the steady photolysis of HN_3 + 2,3-dimethylbutene-2:



This was found to be the case. Furthermore, in the reaction between NH and butene-1 addition at the 2-position produced C_2H_5CN and CH_3CN in almost equal amounts, suggesting that the intermediate formed after 1,3 hydrogen transfer had a lifetime long enough to permit vibrational relaxation. In addition, flash and slow photolysis of ethyl azide vapor, $C_2H_5N_3$, gave similar results to the ethylene -NH reactions, suggesting that the same intermediate nitrene was being formed in both cases. Flash photolysis gave HCN, CH_3CN (ratio$\sim$.9), H_2, CH_4 and a white solid. Steady irradiation gave CH_3CN, CH_4, H_2 and a polymeric gum. HCN seems to react in forming the gum. No ethyleneimine, or ethylamine, which result from solution photolysis of $C_2H_5N_3$,[9] were found.

Lwowski and co-workers have considered in detail several alternative explanations which may also be used to rationalize their results:

The possibility exists for the formation of nitrogen atoms from HN_3. Indeed, the energy requirements of the process $HN_3 \rightarrow H\cdot + \cdot N + N_2$ are well within the limits of that supplied by the 2537 Å radiation. Winkler et.al.[10] have proposed a "unified mechanism" for the reactions of nitrogen atoms with simple organic molecules, illustrated here for C_3 molecules:



$$N\cdot + \cdot C_2H_5 \longrightarrow HCN + CH_3\cdot + H\cdot$$

$$N\cdot + CH_3\cdot \longrightarrow HCN + 2H\cdot$$

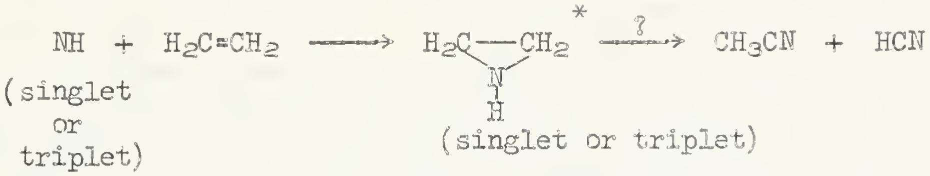
In addition, Dubrin et.al.[11] have studied the reactions of methane and ethylene with ^{13}N atoms produced by nuclear techniques and have concluded that the reaction with ethylene follows the path:

$$C_2H_4 + N(^2D) \longrightarrow HCN + \cdot CH_3$$

Cyanide radicals were ruled out on the basis of results different from the expected $H_2C{=}CH{-}C{\equiv}N/HCN$ ratio of 4-7:1 obtained on addition of ^{11}CN to ethylene.[12] Lwowski and co-workers rule intermediacy of nitrogen atoms in their system out since (1) no emission or absorption bands for triplet N_2 resulting from N atom recombination are observed. (2) There is close correlation of the decay and appearance times of NH and CN respectively, making further dissociation of NH unlikely.

One could argue also that the flash and slow photolyses proceed by entirely

different mechanisms. The only rationale for a common intermediate given by Lwowski is the similarity of products obtained in the flash and slow photolyses and the corresponding photolysis of ethyl azide, differences being primarily due to differences in the energy content of said intermediate depending on its mode of formation. However, there seems to be no evidence at present to rule out the formation of vibrationally excited ethyleneimine followed by decomposition:



However, in analogy to the reaction of methylene with ethylene in the gas phase to produce excited cyclopropane which then isomerizes to propylene, we would also expect excited ethyleneimine to isomerize.

The independent work of two other research groups bears an important relationship to that of Lwowski. Miller and Rice[13] studied the system HN_3-ethylene, analyzing for all products in efforts to obtain a complete mass balance. Products identified were NH_4N_3, ethane, and HCN in comparable amounts, and smaller amounts of H_2 and CH_3CN. Formation of NH_4N_3 in reactions of NH with both alkanes and alkenes suggests the competing sequence:

$$\begin{gathered} NH + C_2H_4 \text{ (or other H atom donor)} \longrightarrow NH_2 + C_2H_3\cdot \\ NH_2 + C_2H_4 \text{ (or other donor)} \longrightarrow NH_3 + C_2H_3\cdot \\ NH_3 + HN_3 \longrightarrow NH_4N_3 \end{gathered}$$

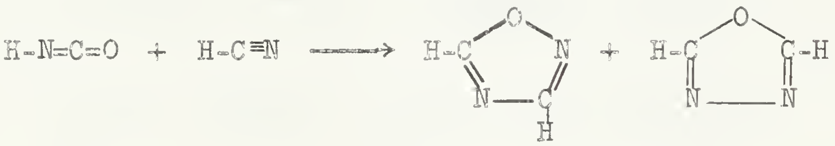
In a series of three papers Back[14-16] and co-workers have analyzed the flash and slow photolysis of isocyanic acid vapor, H-N=C=O, in the presence and absence of various hydrocarbons. A priori the photolysis of HNCO and HN_3 should be related in the same way that reactions of the two methylene precursors ketene, CH_2=C=O, and diazomethane CH_2N_2 are related. At low pressures the photolysis of isocyanic acid gave CO, N_2 and small amounts of H_2 as non condensable products.[14] Although CO_2, HCN, C_2N_2, NO, N_2O and NO_2 could have been detected, they were not found. Small amounts of NH_3 and N_2H_4 were detected also. The mechanism proposed accounted for most of the observations:

$$\begin{aligned} &HNCO \xrightarrow{h\nu} NH + CO \\ &NH + HNCO \longrightarrow NH_2 + NCO \\ &NH_2 + HNCO \longrightarrow NH_3 + NCO \\ &2NCO \longrightarrow N_2 + 2CO \end{aligned}$$

The observation that added ethylene reduced the yield of CO, N_2 and H_2 was accounted for by the scavenging of the initially formed NH by the ethylene.

Lwowski has given three alternative explanations in the light of his studies to account for Back's failure to observe HCN:

(1) HCN produced from the added olefins reacts with HNCO:



oxadiazoles

(2) NH reacts rapidly with HNCO to give •NCO which then attacks ethylene:

$$\cdot NCO + H_2C{=}CH_2 \longrightarrow O{=}C{=}N\text{-}CH_2CH_2\cdot$$

(3) HNCO forms a relatively long lived excited state which reacts with C_2H_4 to give ethyl isocyanate faster than it dissociates.

Brash and Back[16] have carried out a more detailed study of the steady irradiation of HNCO vapor in the presence of olefins and paraffins. Increased amounts of olefins reduced the N_2 and H_2 quantum yields to zero and the CO yield to a constant value indicating complete scavenging of NH radicals. No imines, amines, or other nitrogen

containing products could be found. HCN was again not detected. HNCO irradiated with up to 500 mm of butene-2 gave no HCN or imines. The results were explained on the basis of rearrangement and polymerization of highly vibrationally excited intermediates although no specific analysis of polymeric products was made. Photolysis of HNCO in the presence of ethane, propane, and neopentane showed the same general behavior except that the hydrogen yield increases, and products of radical coupling are found. Small amounts of added ethylene reduce the H_2 yield drastically, presumably by efficient scavenging of H atoms. Photolysis of DNCO-C_3H_8 mixtures and HNCO-D_3H_8 mixtures gave primarily HD, showing that each molecule of H_2 contained one hydrogen atom from HNCO and one from propane. Insertion of NH into a C-H bond to give a vibrationally excited amine was proposed as the most likely process leading to product formation; however, production of hydrogen atoms by this process seems unlikely and other alternative mechanisms cannot be ruled out by the data.

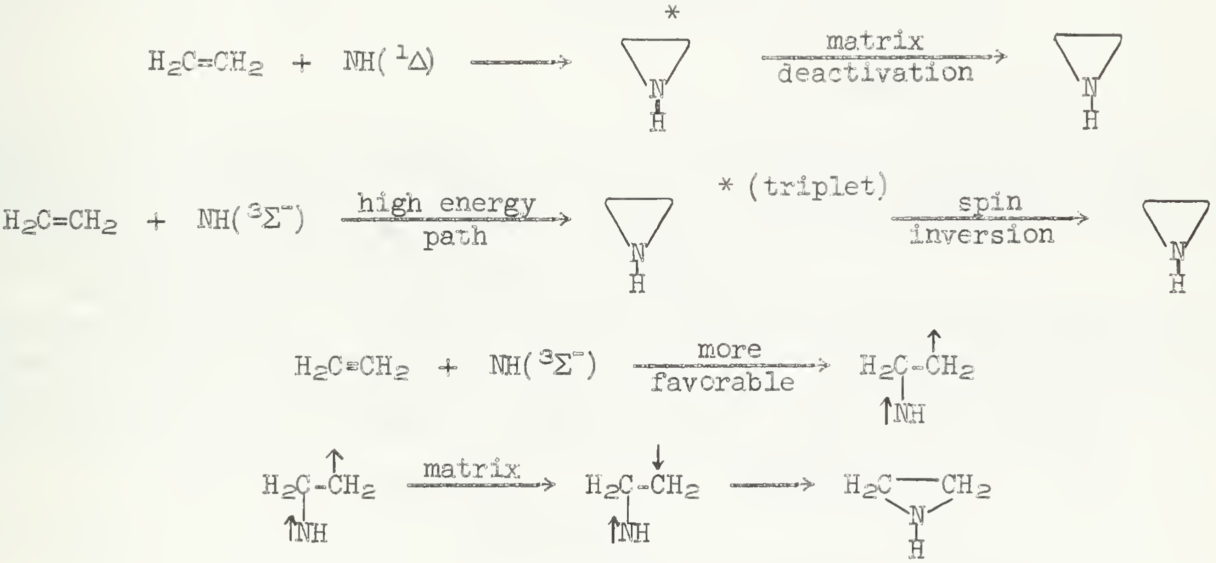
REACTIONS OF NH RADICALS IN THE SOLID PHASE

The stabilization of reactive species and their subsequent reactions in solid matrices at low temperatures have been reviewed in a recent seminar.[17] Briefly reviewing some of the main differences between gas phase and matrix reactions, we find the following:

(1) Severe translational limitations exist for species formed in a matrix; diffusion out of the matrix "cage" is severely limited for all but the smallest of molecules or radicals.

(2) Molecules or radicals formed in excited electronic and/or vibrational states by photolysis or combination with other reactive species may be rapidly converted to lower energy electronic and/or vibrational states by frequent collisions with the inert matrix cage molecules. Alternatively, the matrix cage may be a reactive molecule which can efficiently add to and trap a reactive intermediate.

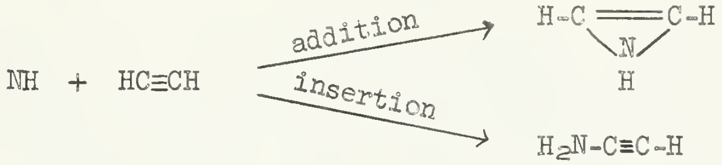
An early study by Milligan and Jacox[18] attempted to correlate reactions of CH_2 and NH in inert argon matrices. Infrared spectroscopy was used to directly analyze the products from the photolysis of mixtures of HN_3-ethylene-argon and HN_3-acetylene-argon at 4°K. The spectral analysis of the HN_3-ethylene-argon system shows that ethyleneimine is the sole product in the matrix. This product could conceivably arise from singlet or triplet NH reacting in the matrix.



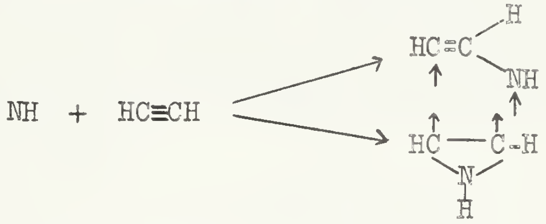
The last pathway is probably more likely since NH should readily be deactivated to the triplet ground state by matrix collisions. However, there is no experimental evidence other than Lwowski's spectroscopic results in the gas phase which allows one to distinguish unambiguously between the three pathways. Matrix photolysis of HN_3-cis-2-butene and/or HN_3-trans-2-butene might help establish the identity of the reacting species. Experiments with methylene from photolysis of diazomethane[19] have shown that it is initially formed as an excited singlet which is subsequently deactivated to the lowest singlet and after an order of magnitude more collisions, to the ground triplet. Addition of triplet CH_2 to ethylene followed by spin inversion

accounts for formation of cyclopropane in matrix reactions to be contrasted with exclusive propylene formation in the gas phase[3] where vibrationally excited singlet cyclopropane is initially produced, then rearranges.

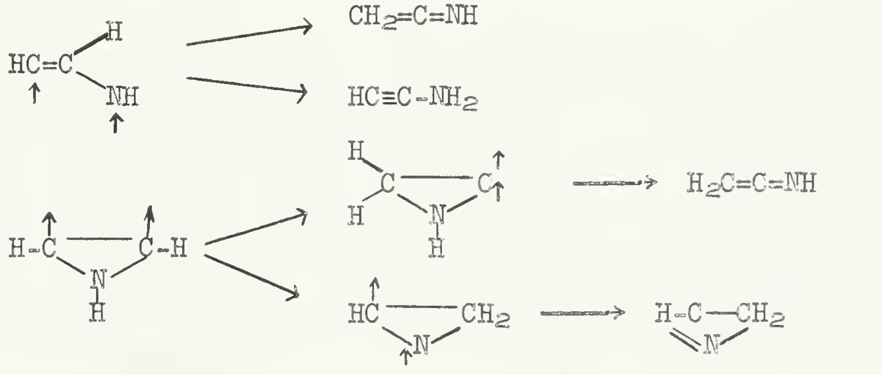
A somewhat more interesting result is obtained in the HN_3-acetylene-argon photolysis. Singlet NH would be predicted to react as follows:


NH + HC≡CH
addition
insertion
H-C═C-H
N
H
H2N-C≡C-H

These species could undergo further rearrangement to acetonitrile or methyl isocyanide. Triplet NH could add in the following manner:


NH + HC≡CH
HC=C
H
NH
HC
C-H
N
H

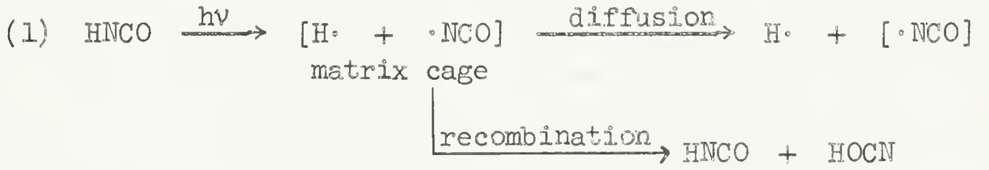
These products could further rearrange:


HC=C
H
NH
CH2=C=NH
HC≡C-NH2
H-C
C-H
N
H
H
C
C
H
N
H
H2C=C=NH
HC
CH2
N
H-C—CH2
N

azacyclopropene

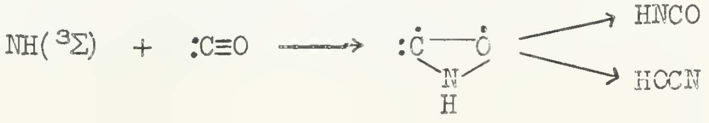
The infrared spectral analysis rules out aminoacetylene, acetyleneimine, and azacyclopropene. The same data strongly indicate the presence of acetonitrile and methylisocyanide as well as the previously unobserved species keteneimine, suggesting that both singlet and triplet NH could be presnet. The analogous matrix reaction of CH_2 with acetylene produces allene almost exclusively.

The photolysis of HNCO and DNCO in argon and nitrogen matrices at 4° and 20°K has been carried out.[20] Infrared analysis reveals results quite different from those obtained in the gas phase in that little NH or CO is spectroscopically detectable and assignment of new bands seems consistent with the species H-O-C≡N. Two mechanisms, each assuming a different primary process, are proposed:


(1) HNCO
hν
[H· + ·NCO]
matrix cage
diffusion
H· + [·NCO]
recombination
HNCO + HOCN

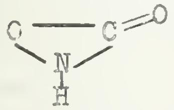
In this scheme, enough H atoms should escape the cage to make ·NCO observable by IR spectroscopy; however, no ·NCO is observed by infrared spectral analysis.

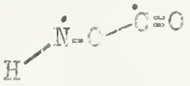
$$(2)\quad \text{HNCO} \longrightarrow [\text{NH} + \text{CO}]$$

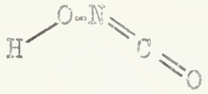

NH(3Σ) + :C≡O
:C—O
N
H
HNCO
HOCN

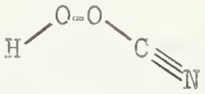
Evidence for the second pathway is given by the fact that in a separate experiment photolysis of an argon-CO-HN_3 mixture gave good yields of both HNCO and HOCN. Analogous to this reaction in carbene chemistry is the photolysis of $N_2 + CO + CH_2N_2$ in a matrix at 20°K with the production of high yields of ketene.[3]

When HN_3 is photolyzed in a matrix composed of solid CO_2 and the product analysis is carried out by direct infrared analysis on the matrix, two distinct groups of bands are observed.[21] One group increases in intensity during the irradiation, the second group rapidly reaches a maximum, then decreases. Control experiments showed that NH radicals did not diffuse through the CO_2 cage to give spectroscopically observable amounts of NH_3. Photolysis of HN_3 in an N_2O matrix gave group I bands but none of the second group, indicating that the latter arose from an intermediate NH-CO_2 adduct. Further analysis identified group I bands as H-N=O. The characteristic absorptions of CO were also identified in the CO_2 matrix. Isotopic substitution using $C^{13}O_2$ and CO_2^{18} showed definitely that a carbon containing species was responsible for group II bands. The observation of pairs of bands with different growth rates in similar regions of the transient spectrum strongly suggests rapid rearrangement of the initial intermediate or formation of an intermediate capable of cis-trans isomerization. Possible intermediates are the following:


(a)


(b)


(c)


(d)

Analogies for (a) exist in the reaction of CH_2 with CO_2 in a matrix,[3] (b) could undergo a cis-trans isomerization about the N-O bond analogous to alkyl nitrites. Structure (c) is ruled out by the infrared analysis and the fact that there was no comparable product (glyoxal) produced in the CH_2-CO_2 reaction. Rearrangement to (d) would involve unfavorable movement of heavy atoms rather than simple hydrogen transfer.

Interesting insight into the reacting NH species in matrix reactions may be given by the photolysis of mixtures of HN_3 and O_2 in solid nitrogen at 20°K.[22] Infrared analysis of the products formed indicates that both cis and trans nitrous acid, HO-N=O are initially formed which undergo further trans→cis isomerization by UV radiation and cis→trans isomerization by the infra-red beam of the spectrophotometer. Evidently NH readily reacts with O_2 to produce HONO. However, the alternate sequence

$$HN_3^* + O_2 \longrightarrow HONO + N_2$$

could not be ruled out at the time. Reactions of CH_2 in the gas phase are not affected by added O_2 except when high pressures of inert gas are used, indicating that singlet → triplet deactivation occurs by collision with the gas, the reaction of triplet CH_2 with oxygen then occurring readily.

LIQUID AND SOLUTION PHASE REACTIONS INVOLVING NH RADICALS

It appears that the evidence involving NH formation in solution reactions of organic molecules is less conclusive than in the gas and solid phase reactions discussed thus far. There are three reagents, the decompositions which in solution phase are proposed in some cases to produce NH radicals. These are (1) hydrazoic acid or azide ion under appropriate photolytic conditions (2) hydroxylamine-O-sulfonic acid H_2N-O-SO_3H under alkaline conditions, and (3) chloramine, H_2NCl, under alkaline conditions. We shall take each of these reagents in turn and compare examples where NH has been considered an important intermediate with those where intermediacy of NH radicals has more or less conclusively been ruled out.

The thorough work of Burak and Treinin[23] has shown that NH radicals can indeed be produced in solution. The photolysis of degassed aqueous solutions of NaN_3 with 2537 A° light produces N_2, NH_2OH, H_2, NH_3 and N_2H_4. Added NH_3 causes a large increase in the N_2H_4 yield, paralleled by a corresponding decrease in the NH_2OH yield. The following mechanism was proposed by the authors to account for the results:

$$N_3^- \xrightarrow{h\nu} N_3^{-*}$$

$$N_3^{-*} + H_2O \longrightarrow HN_3^* + OH^-$$

$$HN_3^* \longrightarrow NH + N_2$$

The ultimate fate of the NH radicals is represented in the following scheme:

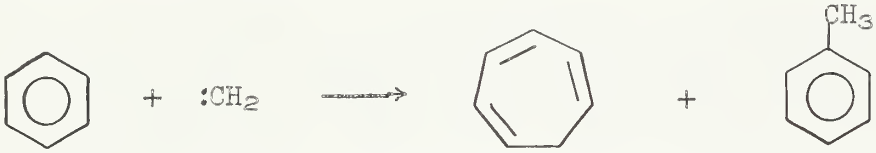
$$NH + H_2O \longrightarrow NH_2OH$$

$$H_2O + NH + N_3^- \longrightarrow N_2 + N_2H_2 + OH^-$$

$$2N_2H_2 \begin{array}{l} \nearrow N_2H_4 + N_2 \\ \searrow HN_3 + NH_3 \end{array}$$

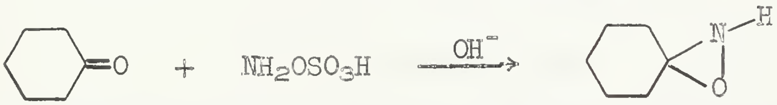
The authors propose that singlet NH is the reactive species, acting as a strong Lewis acid in its reactions with H_2O, NH_3, and N_3^-. The quantum yield of N_2 was not affected by such radical scavengers as N_2O, acetone or methanol-phosphate buffer, which results rule out mechanisms involving chain reactions or solvated electrons. The dependence of the quantum yields of N_2 and NH_2OH on azide ion concentration suggests that there is competition between N_3^- and H_2O for the NH radical. Excess added ammonia also exerts a marked scavenging effect as shown by its effect on the quantum yields. Calculated ratios of rate constants for NH scavenging are $H_2O:NH_3:N_3^- = 1:18:285$. The observations that the quantum yields are independent of the light intensity and that smaller concentrations of impurities including oxygen have no effect on Φ NH_2OH show that the NH radicals produced are quickly scavenged by the large excess of H_2O present.

An early study[24] showed that reactions suggestive of NH formation could be carried out in organic solutions. Hydrazoic acid was irradiated in the presence of toluene solvent to yield presumably mixed toluidines. The isomer ratio was not determined; derivative formation alone was used to confirm the presence of toluidines. The only control reaction run was that of a dark reaction which gave no product formation over a 12 hour period. In a later more systematic study[25] on the solution photolysis of azides, hydrazoic acid was irradiated in the presence of benzene to give low yields of aniline. Photolysis of n-butyl and n-octyl azides in benzene produced comparable amounts of N-n-butyl and N-n-octyl anilines respectively. No mechanisms for these reactions were proposed although presumably if NH and nitrenes were involved, reaction would proceed by insertion of N-H or N-R into a C-H bond. It is interesting that photolysis of diazomethane in benzene solution yields 32% cycloheptatriene and 9% toluene:[3]

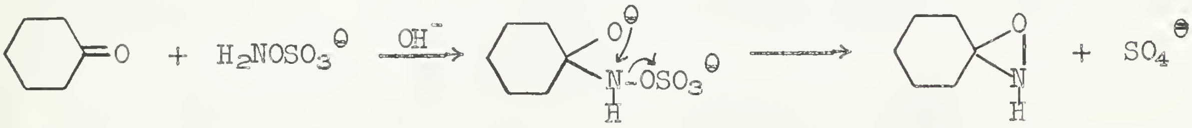


However, none of the analogous ring-expanded product 1-H-azepine was searched for in the corresponding NH experiment.

Hydroxylamine-O-sulfonic acid, $H_2N-O-SO_3H$, has been found to produce some very interesting reactions in recent years, particularly a series of so-called "imination" reactions as illustrated by the following scheme:[26]



Formation of NH followed by addition to the C=O bond could be envisioned. However, the evidence available suggests that reaction takes place through undissociated H_2NOSO_3H.

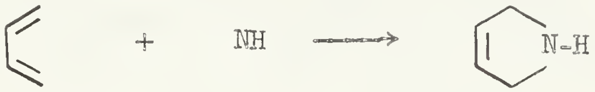


Evidence against dissociation of H_2NOSO_3H to NH radicals is the observation that its rate of reaction in NaOH with various added nucleophiles depends on the nucleophile used which would not be true of NH formation were the rate determining step. Studies of the reaction of HI with H_2NOSO_3H[28] have shown that nucleophilic attack on nitrogen

occurs to give INH_2 initially. Alkyl groups on the nitrogen atom slow the reaction considerably. Thus, a claim that NH from H_2NOSO_3H was trapped by reaction with cyanide ion and precipitated as silver cyanamide[27] may be better explained by direct nucleophilic attack of CN^- on the acid. Furthermore, H_2NOSO_3H does not incorporate radioactive sulfur from radioactive sulfate solutions thus ruling out an initial equilibrium.

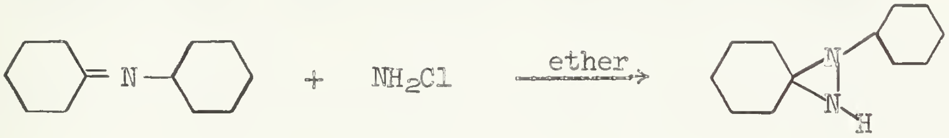
$$H_2NOSO_3^{\ominus} \xrightleftharpoons{OH^{\ominus}} SO_4^{\ominus} + NH$$

In an interesting reaction reported by Appel and Büchner[29] however, we find it hard to rule out direct participation of NH radicals. The reaction of H_2NOSO_3H in sodium methoxide-methanol with butadiene gave a low yield of 3-pyrroline. This result is suggestive of a 1,4 addition of NH:

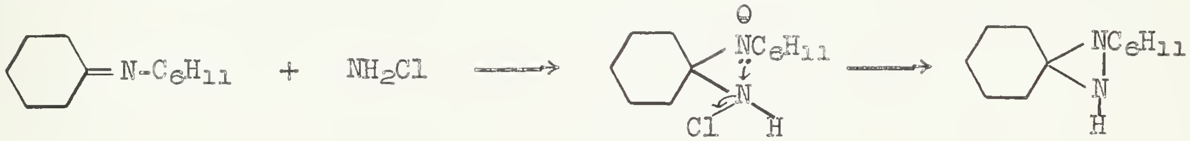


Other added olefins had produced no detectable amounts of aziridines. It is more likely that 1,2 addition of NH actually occurs first followed by rearrangement of the vibrationally excited aziridine to 3 pyrroline. This sequence is not without analogy in carbene chemistry; addition of CH_2 to butadiene in the gas phase produces vinylcyclopropane as the major product and smaller amounts of cyclopentene.[3] The cyclopentene arises presumably from isomerization of excited vinylcyclopropane; at least it has been shown that vinylcyclopropane readily undergoes this isomerization thermally.

Chloramine, NH_2Cl, has also been utilized recently in a number of interesting "imination" reactions.[30]



NH has been shown to be a product of the photolysis of solid chloramine at low temperatures, and of the thermal decomposition of gaseous chloramine. However, in the solution reactions of the compound, the rate of product formation is dependent on the nature of the substrate being attacked, which would not be the case if NH formation were rate-determining. Thus, these reactions seem to proceed by direct nucleophilic additions:[31]



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GEOMETRIC ISOMERISM IN DIAZOKETONES

Reported by Daniel B. Pendergrass April 13, 1967

Although diazoketones (I) were known as early as 1894(1), they were not widely used by the synthetic organic chemist until L. Wolff(2) reported their rearrangement to the corresponding ketenes. This rearrangement is the characteristic step in the Arndt-Eistert synthesis by which a carboxylic acid may be converted to its next highest homolog or one of its derivatives(3).

$R{-}CO_2H \rightarrow R{-}CO{-}Cl$ (a)

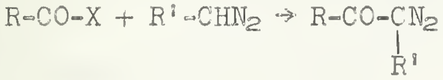
$R{-}CO{-}Cl + 2\ CH_2N_2 \rightarrow R{-}CO{-}CHN_2 + CH_3Cl + N_2$ (b)

$R{-}CO{-}CHN_2 + H{-}R' \xrightarrow{Ag} R{-}CH_2{-}CO{-}R' + N_2$ (c)

$R' = -OH\ ,\ -OR''\ ,\ -NHR''\ ,\ \text{or}\ -NH_2$

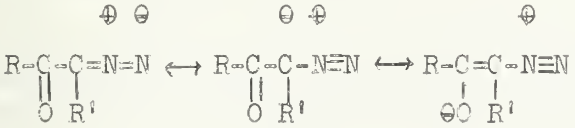
The thermolysis(4,5) and photolysis(5) of diazoketones, as well as their decomposition in the presence of acids(6,7,8), bases(5,9), and various metals (3,5,10) have been discussed. The literature and reactions of diazoöxides have also been reviewed(5,11).

The most widely known synthesis of diazoketones is the reaction of an acyl halide with two equivalents of diazomethane or one of its substituted derivatives. There exists in the literature a variety of representations of the charge distribution and bond orders in these compounds as illustrated below.



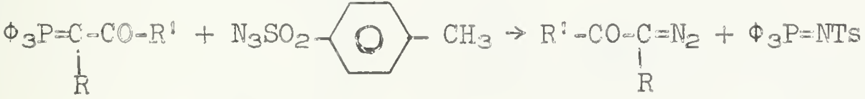
$$R{-}CO{-}X + R'{-}CHN_2 \rightarrow R{-}CO{-}\underset{R'}{\underset{|}{C}}N_2$$

I



$$R{-}\underset{O}{\underset{\|}{C}}{-}\underset{R'}{\underset{|}{C}}{=}\overset{\oplus}{N}{=}\overset{\ominus}{N} \longleftrightarrow R{-}\underset{O}{\underset{\|}{C}}{-}\underset{R'}{\underset{|}{\overset{\ominus}{C}}}{-}\overset{\oplus}{N}{\equiv}N \longleftrightarrow R{-}\underset{\ominus O}{\underset{|}{C}}{=}\underset{R'}{\underset{|}{C}}{-}\overset{\oplus}{N}{\equiv}N$$

These compounds have also been prepared by the oxidation of a monohydrazone of a diketone(12,13,14,15,16,17) obtained in a variety of ways. They are frequently products of nitrous acid oxidation of amines alpha to a -CO-R group (18,19), solvolytic attack on the monotosylhydrazone of a diketone(20,21,22,23,24) in the presence of base, or the action of chloramine or hydroxylamine-O-sulfonic acid on an oximinoketone(25). G. R. Harvey(26) has reported that a series of compounds with structure II react with p-toluenesulfonazide in methylene chloride to give the corresponding diazoketones.



$$\Phi_3P{=}\underset{R}{\underset{|}{C}}{-}CO{-}R' + N_3SO_2{-}C_6H_4{-}CH_3 \rightarrow R'{-}CO{-}\underset{R}{\underset{|}{C}}{=}N_2 + \Phi_3P{=}NTs$$

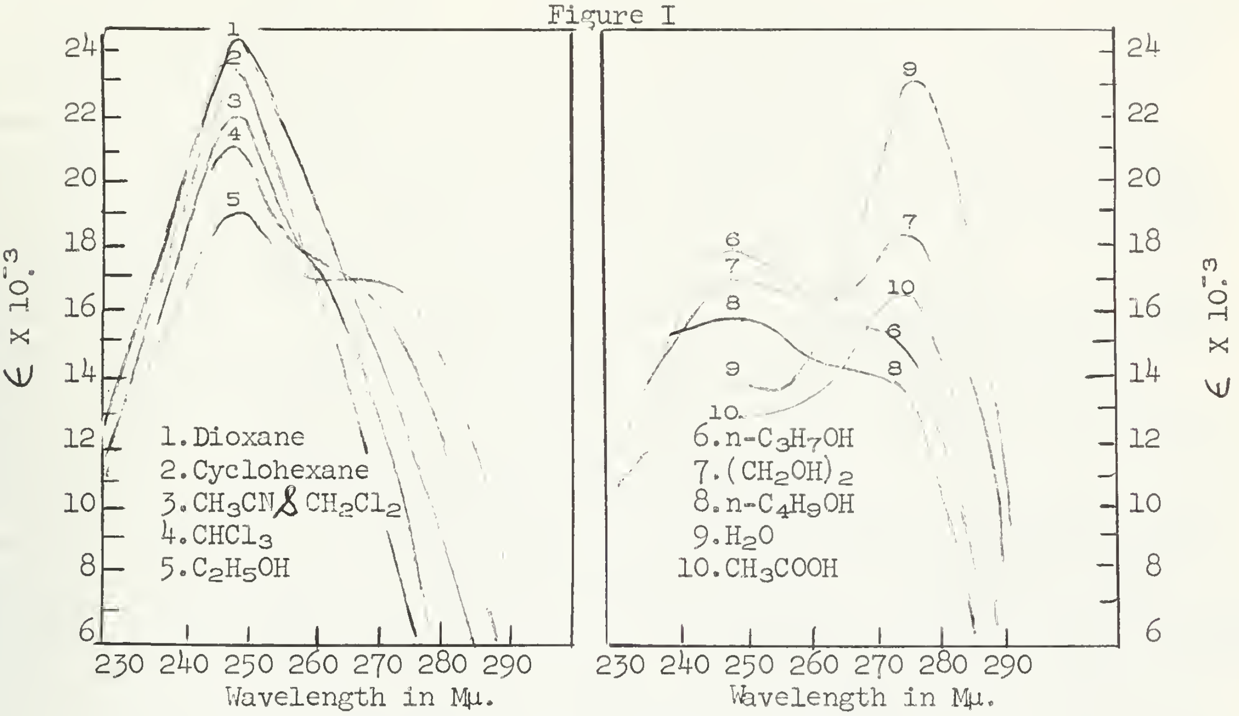
II

Until recently, there were few references in the literature to the absorption spectra of diazocarbonyl compounds(27,28). In the ultraviolet region, there appeared to be a characteristic band at 245-250 mμ for diazoesters and diazoketones(29,30). In the infrared spectra, an abnormally low carbonyl frequency (1630-1660 cm^{-1}) has been attributed to the contributions from the species with the charge distributions shown above. A strong band at 1335-1410 cm^{-1}, not observed in the diazohydrocarbons, must be the symetric stretching mode of =CNN which has been shifted to higher frequency by a high degree of conjugation(31).

Earlier observations of the ultraviolet spectra of diazoketones were confirmed by Miller and White(32) when they investigated the spectra of a series of diazocarbonyl compounds. Solvents were found to have only a slight effect in most of the cases considered. However 1,8-bisdiazo-2,7-octanedione (III) gave two bands, one at 247 mμ and another at 273 mμ. The 247 mμ band is observed in nonhydroxylic

solvents. In hydroxylic solvents, the band at 247 mμ is weakened and a second band at 273 mμ appears. See Figure I(32). The energy difference is about 11 kcal/mole between the two bands. A difference of 25 mμ is much larger than the 5-10 mμ solvent shift normally observed(33).

Figure I



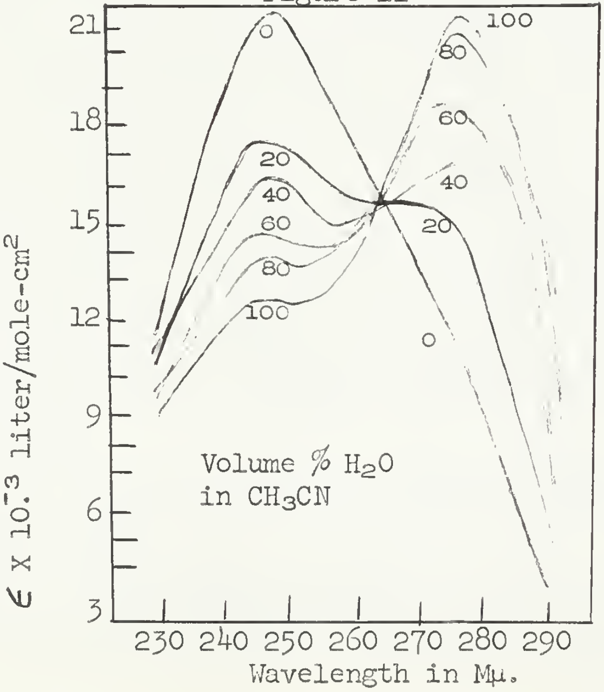
Ultraviolet spectra of III

$N_2CH-CO-(CH_2)_4-CO-CHN_2$ III

$N_2C(CH_3)-CO-C(CH_3)_3$ IV

In a series of mixtures of acetonitrile and water, the relative intensities of the two peaks shift smoothly with only a very slight change in the frequency of either band. The same curves are obtained if water is added to the acetonitrile solution or vice versa, Fig. II. This family of curves passes through an isosbestic point which constitutes proof of an equilibrium between the two molecular species responsible for the bands(34,35). The fact that the curves do not form a perfect isosbestic point has been attributed to the superposition of changes in the refractive index of the solvent on the shift(32).

Figure II



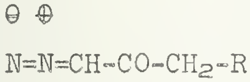
Spectrum of III in mixtures of water and acetonitrile. Numbers are the volume percent of water.

Similar plots were also obtained by Fahr(36) for several diazoketones and diazoesters in a series of dioxane-water mixtures.

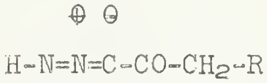
The possibility of a keto-enol tautomerism was considered first. Miller and White(32) prepared a series of diazoketones with substituents at the positions α and α' to the carbonyl. The compound (IV) chosen to represent the case with no hydrogens available for enol formation was, unfortunately, unstable. In each of the four solvents chosen, it gave a band at 290-304 mμ which increased in intensity with time and was attributed to decomposition products. The major absorption at 247-249 mμ was always present, but there was no band at 273-275 mμ. Those compounds of the series having enolizable hydrogens gave both bands in the expected manner. Bromine could not be used to test for a keto-enol tautomerism because diazoketones decompose in its presence.

Examination of the infrared spectra of these compounds showed no hydroxyl band at 3200-3400 cm^{-1} in nonhydroxylic solvents. In hydroxylic solvents, where the enol should be most prevalent, the solvent masked the region of interest. The carbonyl absorption of III is found at 1640 cm^{-1} in methylene chloride. It shifts to 1625 cm^{-1} in n-butanol, but it retains the same intensity. Since this shift may be due to the difference in solvent effects, it does not prove that the enol does not exist, but it argues against this possibility.

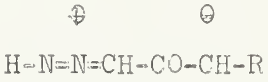
Turning to the diazo band at 2090 cm^{-1}, they noted that the integrated intensity was 21% less in n-propanol than in methylene chloride. This corresponds to a 20% reduction observed in the ultraviolet spectra. On this basis, they postulated the existence of a diazo-isodiazo tautomerism, citing the observation of similar forms in diazohydrocarbons(37). The structure Va could then be assigned to the absorption at 247 mμ, while the peak at 275 mμ could be attributed to Vb or Vc either of which should show a =N-H band at 3300-3400 cm^{-1}. As in the case of the keto-enol tautomerism, the nature of the solvents hides the region of the spectra which would provide proof of the presence of the postulated equilibrium.


$\overset{\ominus}{N}=\overset{\oplus}{N}=CH-CO-CH_2-R$

Va


$H-N=\overset{\oplus}{N}=\overset{\ominus}{C}-CO-CH_2-R$

Vb


$H-N=\overset{\oplus}{N}=CH-CO-\overset{\ominus}{CH}-R$

Vc

In 1959, Fahr (36) reported the spectra of a number of diazocarbonyl compounds, both diazo ketones and diazoesters, which had no hydrogens available for either of the tautomerisms described above, but which still exhibited an isosbestic point in dioxane-water mixtures. He suggested that a hydrogen bonded complex was formed between the solvent hydroxyl and the carbonyl of the diazocarbonyl compound. This is not entirely satisfactory, because it requires that the intensity of the carbonyl remain constant in spite of the hydrogen bond formation and also that the intensity of the diazo band be lowered by reduction of the double bond character of the carbon-nitrogen bond.

Foffani and co-workers(38) entered the discussion in 1964 with a study of the infrared spectra of diazoacetophenone and its derivatives in a variety of solvents. They also ruled out the possibility of a keto-enol tautomerism on the basis of the invariance of the carbonyl intensity. For diazoacetophenone, the diazo nitrogen-nitrogen stretching frequency does not change (2108-2112 cm^{-1}) over the solvent range investigated. See Table I. The integrated intensity of this band is also nearly independent of solvent. Changing from apolar to polar solvents or from apolar to commonly hydrogen bonded solvents does cause the half width to increase.

From this data and the fact that some of their substituted diazoacetophenones had no hydrogens available but still gave an isosbestic point, they also ruled out a diazo-isodiazo tautomerism.

To test the hydrogen bonded complex suggested by Fahr, they examined the behavior of the phenolic hydroxyl group absorption in solutions containing diazoacetophenone. With a diazoketone:phenol ratio of 20:1, they found only normal hydrogen bonding to the carbonyl. Similar results were observed with ratios of

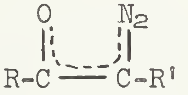
Table I

Solvent	ν NN	$\Delta\nu_{1/2}$	$\epsilon_{max} \times 10^{-3}$	$A_{NN} \times 10^{-4}$
hexane	2108	11	1.27	5.4
CCl_4	2108	14	1.12	5.8
C_2Cl_4	2108	13	1.15	5.2
CH_2Cl_2	2109	18	0.93	6.0
$CHCl_3$	2111	18	0.87	5.6
n-butanol	2112	18	0.75	5.9
CH_3NO_2	2108	22	0.91	6.1

A_{NN} is the integrated intensity in liter/mole-cm^2.

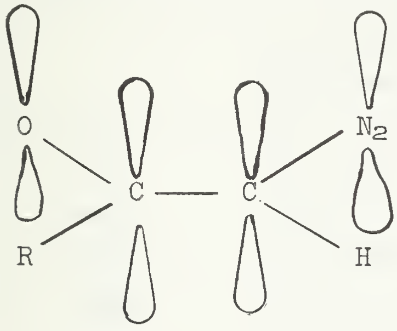
10:1 and 1:1. In these cases, as well as those in which the phenol concentration would be too low to form appreciable adduct, a second type of carbonyl was detected.

Having disproved each of the three possibilities presented thus far, they suggested a rotational isomerism. The rotational isomers' stability could be affected by the intermolecular interactions with the carbonyl. The spectral data presented are consistent with this view. In addition, the low carbonyl frequency suggests a form such as VI, as does the broadening of the nitrogen-nitrogen stretching band. They note that diazoöxides, in which rotation is not possible, show only one band in the ultraviolet, that at 245-250 mμ.

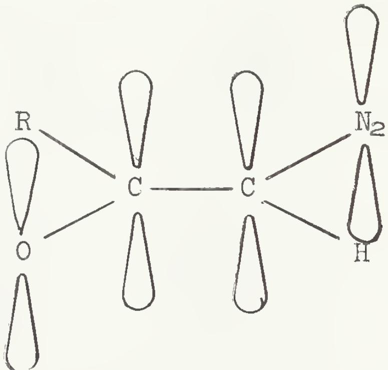


VI

In a preliminary communication and later in a paper(39,40), Kaplan and Meloy reported the temperature dependence of the n.m.r. spectra of diazoketones. Previous investigations(41,42,43) had been made of the *cis* and *trans* isomers arising from restricted free rotation about the central C-N, O-N, or N-N bond of amides, nitrites, and nitrosoamines. A similar situation is possible for diazoketones. Rotation about the central C-C bond may be restricted by interaction of the lone pair of the α carbon with the π system of the carbonyl. This should give rise to two isomers of the diazoketone which may be designated *cis* or *trans* from the geometry of the π system.



cis



trans

The temperature dependence of the n.m.r. spectra confirmed the existence of an equilibrium. At 30°, the spectrum of diazoacetaldehyde consists of two broad singlets. Raising the temperature to 71° causes both the methine and aldehyde protons to exhibit time average doublets with a coupling constant of

2.2 cps. At or below 8°, each region of the spectrum contains a singlet and a doublet ($J = 7.5$ cps) in a 7:3 ratio. In the methine region, the singlet is at lower field than the doublet. For the aldehydic proton, this is reversed. Other alkyl diazoketones, for example, diazoacetone, exhibit similar behavior. At 30°, they have a single methine signal that broadens as the temperature is lowered until, at some temperature, the methine peak splits into a low field singlet and a higher field doublet. The intensity of the singlet is usually about nine times that of the doublet. In the ten compounds reported, the low temperature cis:trans ratio varied from 9:1 to 1:1. A shift to lower field at lower temperatures was observed and attributed to hydrogen bonding. The relatively unhindered cis compounds showed a greater shift than that found for the trans.

Several aryl diazoketones exhibited only a slight broadening at the lowest temperature at which they were examined. In addition, 1-diazo-3,3-dimethyl-2-butanone showed no broadening over a 70° range. Diazoesters have the same type of temperature dependence as diazoketones, but they do not show two methine peaks until lower temperatures are reached(-30° to -50°).

The methine region was chosen for study because it was free from other absorptions, showed the greatest chemical shift difference between the cis and trans form at low temperatures, and because it was a part of the constant structural feature of these compounds. Both the keto-enol and the diazo-isodiazo tautomerisms may be eliminated from consideration by the fact that the $^{13}C-^{1}H$ coupling constant ($J = 199$ cps) for the methine proton in the time-averaged species and that of the major species at low temperatures are the same for alkyl diazoketones. In the case of either tautomerism, the same coupling constant would not be observed for the time-averaged species because the exchange of protons would average out. This feature of the spectra argues that the C-H bond is essentially unchanged during the equilibrium. Thus the case for rotational isomerization is confirmed.

Because the spin-spin coupling constant of trans protons is expected to be much greater than that for cis protons in such a system, (33,44,45) the low field methine singlet ($J < 0.3$ cps) may be assigned to the cis form while the doublet is assigned to the trans species. Calculations based on the resonance lines of the methine region were used to obtain the relative populations of the two isomers, their mean lifetimes(46), and the activation energies for conversion of the isomers.

Table II(40)

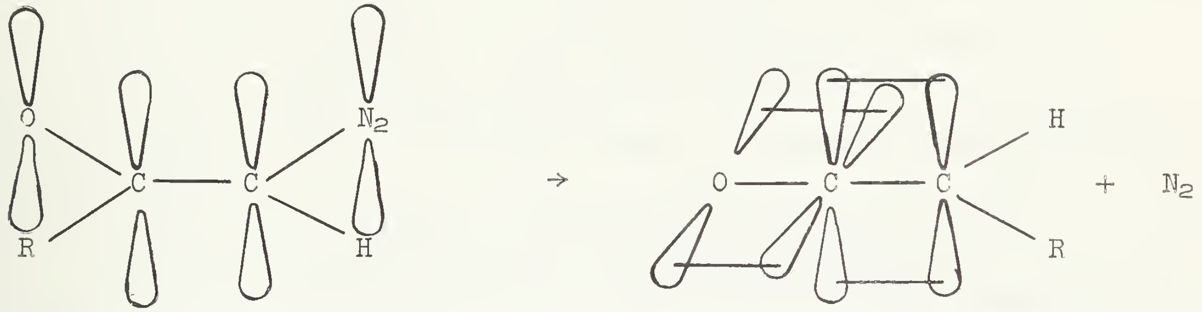
The Equilibrium Constants, Standard Free Energy Difference Between the cis and trans Forms, the Energy of Activation, and Temperature of Coalescence, T_c, for Diazoketones: $RCOCHN_2$.

R	K_{eq} (cis→trans) ~~kcal/mole~~	ΔF kcal/mole	K_a kcal/mole	T_c, °C
CH_3	0.082(-40°)	1.16	15.5 ± 0.9	13.9
C_2H	0.063(-40°)	1.28	16.2 ± 0.6	6.5
ΦCH_2	0.040(-40°)	1.49	18.2 ± 0.6	1.0
CH_3O	0.859(-50°)	0.07	12.5 ± 0.9	-25.0
C_2HO	0.840(-50°)	0.08	9.0 ± 0.8	-32.5

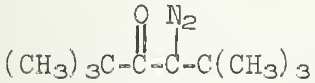
The existence of this cis-trans isomerism must be taken into account when describing the mechanisms of the reactions of diazoketones since it may direct the course of the reaction. If the rate of interconversion of the two isomers is faster than the rate of reaction, this will not be a consideration.

The demonstrated preference of diazoketones for a cis configuration leads one to consider the possibility that the Wolff rearrangement to ketenes may proceed through a smooth concerted process in which the migrating group is trans to the leaving group. See Figure III. If the rearrangement takes place by initial carbene formation, there would be no preference for geometry. Evidence may be presented for both mechanisms. The appearance of hydroxy ketones in the decomposition of some diazoketones in water would be more likely to occur by hydrolysis of the carbene than directly from the diazoketone(47).

Figure III

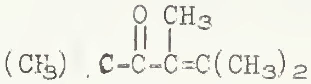


On the other hand, decomposition of VII under thermal, photolytic, or copper-catalysed conditions(15) leads to VIII in 80-92% yield with very little of the rearrangement product IX. Models of the cis form of the diazoketone (VII) are very hard to make because of the large steric interaction of the t-butyl groups. Since the compound exists almost entirely in the trans form, the rearrangement process postulated above could not readily take place.



$(CH_3)_3C-\overset{\overset{O}{\|}}{C}-\overset{\overset{N_2}{|}}{C}-C(CH_3)_3$

VII

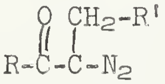


$(CH_3)_3C-\overset{\overset{O}{\|}}{C}-\overset{\overset{CH_3}{|}}{C}=C(CH_3)_2$

VIII

$((CH_3)_3C)_2C=C=O$

IX

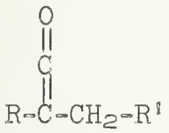


$R-\overset{\overset{O}{\|}}{C}-\overset{\overset{CH_2-R'}{|}}{C}-N_2$

X

R-CO-CH=CH-R'

XI



$R-\overset{\overset{\overset{O}{\|}}{C}}{\overset{\|}{C}}-CH_2-R'$

XII

For X, XI, and XII

R	R'
Φ-	H-
p-$NO_2\Phi$	H-
Φ-	CH_3-
p-$CH_3O\Phi$-	CH_3-
p-$NO_2\Phi$-	CH_3-
p-$Cl\Phi$-	CH_3-

In a similar manner, X undergoes photolytic and silver oxide catalyzed decomposition to XI at room temperature, but gives appreciable amounts of XII at elevated temperatures(48). The cis form may be more prevalent if the additional thermal energy is sufficient to overcome the steric interactions.

Summary

The possibilities of both keto-enol and diazo-isodiazo tautomerisms in diazoketones have been investigated. They were found to be unlikely. To explain the persistence of spectral data for an equilibrium in solutions with hydroxylic solvents, a hydrogen bonded complex was postulated. This was also shown not to be the case. The existence of a cis-trans isomerism has been demonstrated, and found to be consistent with spectral data.

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E.S.R. STUDIES OF ORGANIC GROUND-STATE TRIPLET MOLECULES

Reported by Robert J. Basalay April 17, 1967

INTRODUCTION

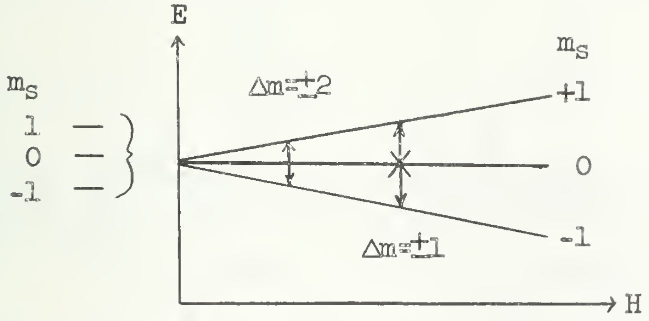
The following discussion of triplet-state molecules will be confined to molecules which exist as triplets in their ground-states or are in equilibrium with ground-state singlet species. The use of esr spectroscopy to observe triplet-states, and the results of its use to observe the triplet-states of diradicals, methylene derivatives, and π-electron triplets will be discussed. A diradical is properly defined as a molecule with two unpaired electrons whose centers of gravity do not coincide, but here the term is used to indicate molecules with two unpaired electrons localized on different atoms which may or may not interact to give a triplet-state.

THE TRIPLET STATE[1,2]

The two spin states of an electron can be represented by the spin quantum numbers, $m_s=\pm 1/2$. If more than one electron is involved, the spin states are represented by the total spin quantum number, S, given by $S=\left|\sum_i (m_s)_i\right|$. If two electrons have their spins parallel in a given state, $S=|(m_s)\text{electron 1} + (m_s)\text{electron 2}|=1$. The degeneracy of a state due to electron spin is given by $2S + 1$. The S=1 state is triply degenerate and a triplet state. If the electrons are antiparallel, S=0 and it is a singlet state.

Two factors determine whether the ground state of a molecule is a singlet or a triplet, the orbital energies and the strength of the exchange interactions between electrons of parallel spin. If we have two degenerate orbitals, the triplet state is always lower in energy because of the exchange interactions; but if the orbitals are of different energy the two electrons may be found paired in the orbital of lowest energy, to form a singlet state. A competition between the energy separation of the orbitals and the energy gained by having parallel spins determines whether a molecule exists as a ground-state triplet or singlet. If the two factors are comparable, a thermal equilibrium will exist with comparable amounts of singlet and triplet.

The degenerate triplet state levels can be split by an external magnetic field (the Zeeman effect). The triplet levels have the spin quantum numbers $m_s=1,0,-1$ associated with them. When the levels are split, there are two possible esr transitions, $\Delta m=\pm 1$ and $\Delta m=\pm 2$. However, the selection rule for esr transitions is $\Delta m=\pm 1$. Hence, the $\Delta m=\pm 2$ transition is forbidden and only the $\Delta m=\pm 1$ transition would be observed. The resulting spectra would be similar to that of a radical with S=1/2. However, only exchange and electrostatic interactions between electrons have been considered.



If the magnetic dipole-dipole forces between the two unpaired electrons are considered, the degeneracy of the triplet is removed without the application of an external magnetic field (zero-field). When the dipole interaction is considered and zero field splitting of the triplet levels occurs, the "forbidden" $\Delta m=\pm 2$ transitions becomes allowed. The appearance of this transition is not a violation of the usual selection rule, $\Delta m=\pm 1$, because it does not apply at the low magnetic field strength (~1500 gauss, $h\nu=9500$ Mc/s) where the $\Delta m=\pm 2$ transition occurs. Hence, there are two types of transitions in the esr spectra of triplet-states, "$\Delta m=\pm 1$" and "$\Delta m=\pm 2$."

A spin Hamiltonian for the two major magnetic interactions, the electronic Zeeman and the dipolar, of two unpaired electrons within a molecule is $\mathcal{H} = g\beta\vec{H}\cdot\vec{S} + g^2\beta^2\{\vec{S}_1\cdot\vec{S}_2/r^3 - 3(\vec{S}_1\cdot\vec{r})(\vec{S}_2\cdot\vec{r})/r^5\}$ where $\vec{r}$ is the vector joining the two electrons, β is the electronic Bohr magneton. The isotropic electron g factor should be an

anisotropic g tensor, but for most organic triplets the g tensor anisotropy is small and will be neglected here.

The second term of $\mathcal{H}$ is the dipolar interaction term $\mathcal{H}_D$. Expanding $\mathcal{H}_D$ by means of the various vector products and expressing everything in terms of the total spin S, we obtain $\mathcal{H}_D = 1/2g^2\beta^2\{S_x^2(r^2-3x^2)/r^5 + S_y^2(r^2-3y^2)/r^5 + S_z^2(r^2-3y^2)/r^5 - (S_xS_y + S_yS_x)3xy/r^5 - (S_yS_z + S_zS_y)3yz/r^5 - (S_xS_z + S_zS_x)3xz/r^5\}$. This result can be expressed in the matrix form:

$$H_D/(1/2g^2\beta^2) = \begin{pmatrix} S_x \\ S_y \\ S_z \end{pmatrix} \begin{pmatrix} (r^2-3x^2)/r^5 & -3xy/r^5 & 3xz/r^5 \\ 3xy/r^5 & (r^2-3y^2)/r^5 & -3yz/r^5 \\ -3xz/r^5 & 3yz/r^5 & (r^2-3z^2)/r^5 \end{pmatrix} (S_x S_y S_z) = \mathbf{S}\cdot\mathbf{D}\cdot\mathbf{S}$$

D is a symmetric tensor called the zero-field splitting tensor which may be diagonalized by proper choice of coordinate systems. In terms of the new coordinate system (x', y', z'), $X=(r^2-x'^2)/r^5$, $Y=(r^2-y'^2)/r^5$, and $Z=(r^2-z'^2)/r^5$, and the spin Hamiltonian becomes $\mathcal{H} = g\beta\vec{H}\cdot\vec{S}-XS_x^2-YS_y^2-ZS_z^2$. Since the tensor is traceless $(X+Y+Z=0)$, the zero-field splitting can be expressed in terms of just two independent constants, $D=1/2(X+Y)-Z$ and $E=-1/2(X-Y)$, giving $\mathcal{H} = D(S_z^2-1/3S^2) + E(S_x^2-S_y^2) + g\beta\vec{H}\cdot\vec{S}$.

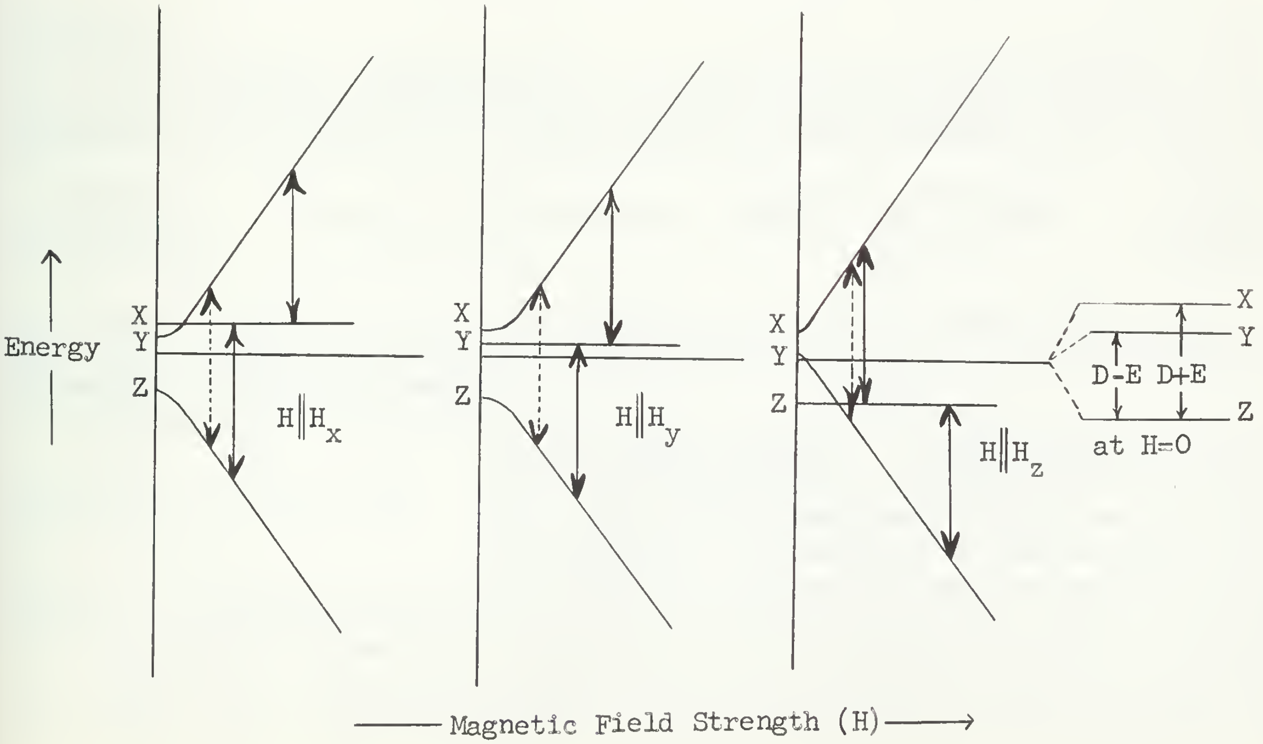
In order to find the energy level splitting in the triplet state due to zero-field splitting, the eigenvalue problem, $\mathbb{H}\Phi = \Phi\mathbb{E}$, must be solved. The spin functions will be chosen to diagonalize the zero-field Hamiltonian matrix where $\Phi = (\phi_x, \phi_y, \phi_z)$. The solution of the eigenvalue problem is given by the matrix, $\mathbb{T}$.

$$\mathbb{T} = \begin{pmatrix} X-E_1 & -ig\beta H_z & ig\beta H_y \\ ig\beta H_z & Y-E_2 & -ig\beta H_x \\ -ig\beta H_y & ig\beta H_x & Z-E_3 \end{pmatrix} = 0$$

If there is no external field $(H_x=H_y=H_z=0)$, the matrix is diagonalized and $E_1=X$, $E_2=Y$, and $E_3=Z$, the energies of the levels of the triplet at zero magnetic field.

If we impress an external magnetic field, H, on our system parallel to the z direction, $H=H_z$ and $H_x=H_y=0$, and the matrix has the following solutions: $E_1=1/2(X+Y) + 1/2(X-Y)\tan\Theta + g\beta H$, $E_2=1/2(X+Y) - 1/2(X-Y)\tan\Theta - g\beta H$, and $E_3=Z$, where $\tan 2\Theta = (X-Y)/2g\beta H$. A set of graphs simulating the zero-field splitting when $H=H_z$, H_y, and H_x is given in Figure 1.

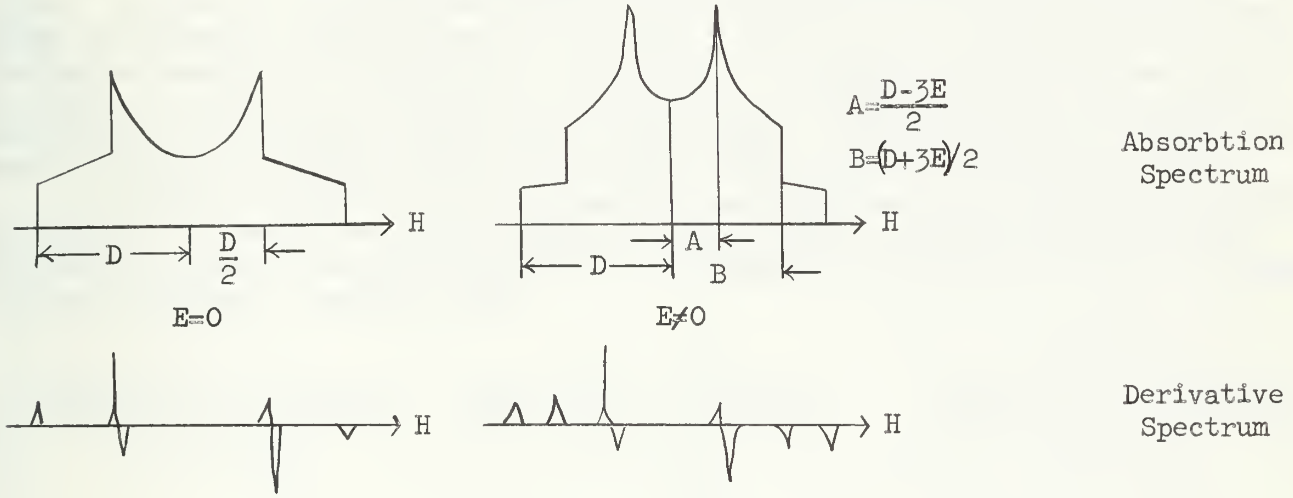
Figure 1 Zero-Field Splitting of Triplet Energy Levels



The arrows in Figure 1 represent electron spin resonance transitions at constant $h\nu$ while varying H.

The esr spectra of a triplet whose molecules were all oriented the same way would have three transitions whose position would vary as the orientation of the triplet with respect to the external magnetic field were changed. An example of this case will be seen when the esr spectrum of diphenylmethylene is discussed. When the triplet molecule is dissolved in a liquid, the rapid molecular tumbling averages out the effect of dipole-dipole interaction on the esr spectra of randomly oriented molecules. When the triplet molecule is frozen in a glass, the effect of the dipolar interaction is not averaged out for the randomly oriented molecules. The intensity of the esr signal is greatest when the external magnetic field is parallel to a principal magnetic axis of the triplet. The derivative curve of an esr absorption spectrum gives special prominence to the magnetic field strengths which cause esr transitions to occur in the molecules which have principle magnetic axes parallel to the external magnetic field. This type of triplet esr spectrum is simulated in Figure 2. Approximate zero-field splitting parameters can be obtained from studies of the $\Delta m = \pm 2$ transitions whose anisotropy is relatively small, allowing them to be easily observed for randomly oriented triplet molecules in frozen matrices.[4]

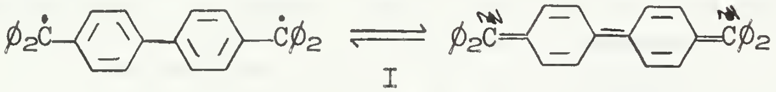
Figure 2. Simulation of ESR Spectra of Randomly Oriented Triplets[3]



DIRADICALS

Certain organic compounds exhibit a chemical behavior characteristic of free radicals, but contain even numbers of electrons. One of these compounds is Chichibabin's hydrocarbon, p,p'-biphenylene-bis-(diphenylmethyl) (I). This compound

Triplet (paramagnetic)

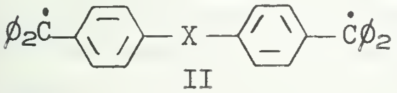


I

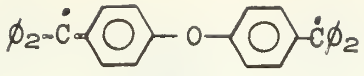
Singlet (diamagnetic)

was thought to exist in two forms, a triplet state and a singlet state. The fact that an esr signal is observed for Chichibabin's radical in solution indicates a paramagnetic species is present.[5]

Another type of diradical (II), where X is a bridging group (i.e. -O-, $(-CH_2-)_n$,), can not have a quinoid singlet state. If there is spin interaction between the two halves of the diradical, there will be a ground-state triplet and an excited-state singlet. If there is no spin interaction, the halves of the molecule will be independent of one another and behave like two mono-radicals. Compounds of this type (II) were examined by Jarrett, Sloan, and Vaughan.[6,7] The sharpness (esr linewidth ∽ 12 gauss) of the esr spectra indicated a comparatively small interaction between the unpaired electrons. The larger the spin interaction, the broader the esr spectrum becomes because the spin-spin coupling produces strong relaxation effects which decrease the relaxation time increasing the esr line-width.



II



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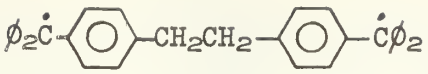

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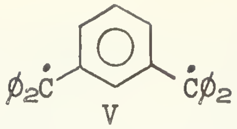
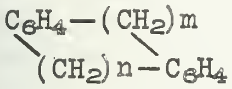


V

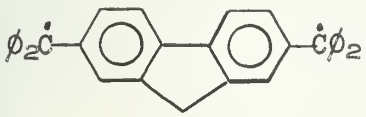
The spin exchange (spin interaction between the two radical centers) in several biradicals (I, III, IV, and V) which were labeled with C^{13} at the triphenylmethyl carbon atoms was studied by means of the resultant nuclear hyperfine splitting observed in the esr spectra. If the spin interaction is large, the esr spectra will show nuclear hyperfine splitting due to two equivalent C^{13} (I=1/2) atoms. This is a triplet-state. If the spin interaction is small, the esr spectra will show nuclear hyperfine splitting due to one C^{13} atom. This is equivalent to a pair of doublets or a triplet with very weak spin interaction. The latter case was observed.

However, Weissman[8] has shown that the electron interaction between the aromatic rings of the anions of paracycloph$\overset{an}{ene}$s (VI), provided n or m is 1 or 2, is large (i.e. the nuclear hyperfine splitting due the hydrogen atoms of both aromatic rings are observed in the esr spectra). If n, m ≥ 3, then the nuclear hyperfine splitting due to the hydrogen atoms in one aromatic is observed in the esr spectra indicating small electron interaction between the aromatic rings. McConnell[9] has performed theoretical calculations for the ground-excited state splittings in large biradicals of this type (II) and according to the calculations a larger spin interaction is indicated. The spin interaction observed for a $-CH_2CH_2-$ bridge (i.e. X in II) is equivalent to a calculated spin interaction resulting from a bridge of about five $-CH_2-$ groups. This discrepancy between the spin interaction observed and that one would expect is the "biradical paradox."

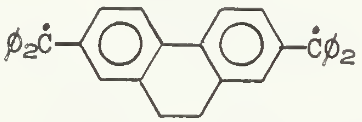


VI

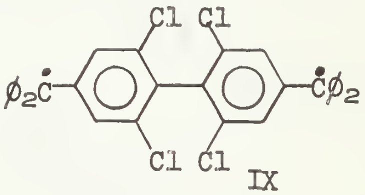
A possible explanation for the smaller than expected spin exchange was offered by Bersohn.[10] One or two $-CH_2-$ groups do not present a serious barrier to the passage of a single electron, but it is a formidable barrier to the spin interaction of two electrons of parallel spin.



VII



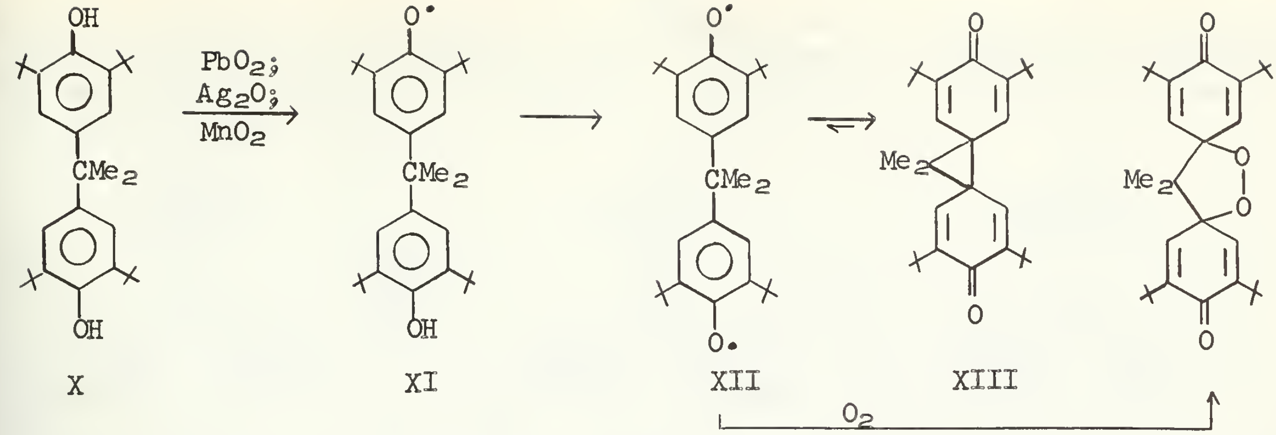
VIII



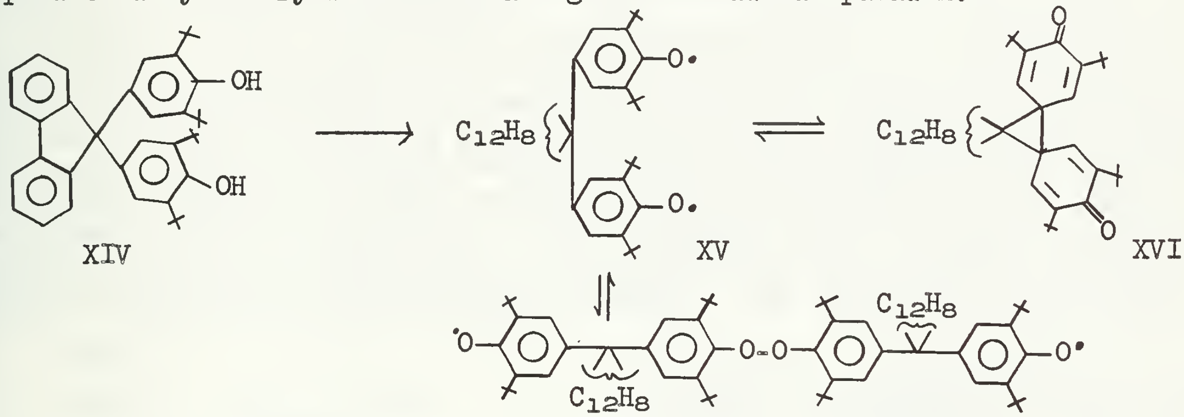
IX

An examination[11] of the esr spectra of compounds I, VII, VIII, and IX indicated that the paramagnetic species in biradical solutions is a dimer or higher polymer. As a result the spin interaction between electrons would be much smaller than would be expected for the monomer. It was found that the room temperature intensity of the esr signal can be maintained at low temperature if the specimen is cooled rapidly enough. If the temperature is lowered slowly the intensity of the esr signal decreases. Also, when the specimen is heated, the esr signal is enhanced. If the heated solution is cooled to room temperature, the esr signal diminishes to a final intensity of slightly less than the starting intensity. If the specimen is cooled to a temperature at which equilibrium is slow, the intensity of the esr signal can be enhanced by illumination. The enhancement persists until the solution is heated to a point where the equilibrium is rapid. Thereupon the intensity diminishes again. These effects indicate that biradical monomers associate in solution to form dimers or polymers.

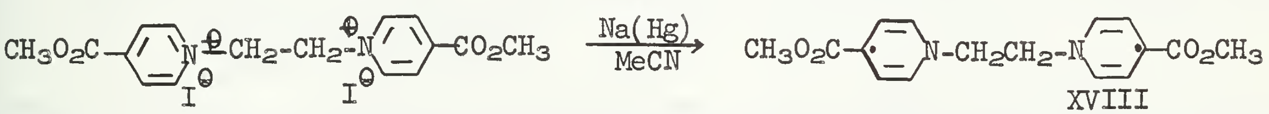
In two communications, Chandross and Kreilick[12] reported attempts to produce a triplet molecule by linking two phenoxyl radicals by a $-CMe_2-$ bridge (XII). No triplet spectra were observed, but chemical and spectral data indicated the reaction scheme on the following page. The infrared spectrum of the oxidation product (XIII) showed no band at 6.4 μ, characteristic absorption of phenoxyl radicals, but there was a doublet, characteristic of this type (XIII) of cyclohexadienone, at 6.08 and 6.16 μ. The presence of the biradical (XII) in equilibrium with XIII is indicated by a rapid reaction of the oxidation product with O_2. The dienone (XIII) would not be expected to react rapidly with oxygen (reaction complete in minutes at room temp.), but the biradical (XII) would.



To make the internal formation more difficult, they then replaced the $-CMe_2-$ group with a 2,2'-biphenylene group (XIV). When XIV was oxidized with aqueous alkaline ferricyanide, the infrared spectrum of the oxidation product in CCl_4 had a pair of strong absorptions at 6.0 and 6.2 μ assigned to XVI and a strong band at 6.4 μ which was assigned to XV. The esr spectrum revealed the presence of triplet species. There were two sets of $\Delta m = \pm 1$ lines as well as a $\Delta m = \pm 2$ transition. The larger splitting was attributed to XV and the smaller was thought to be due to a dimer possibly linked by a peroxide bond (XVII). If this smaller splitting is due to the dimer (XVII), it would indicate that the unpaired electrons can interact relatively strongly across long organic molecules, possibly to the degree which could be predicted by theory without creating the "biradical paradox."



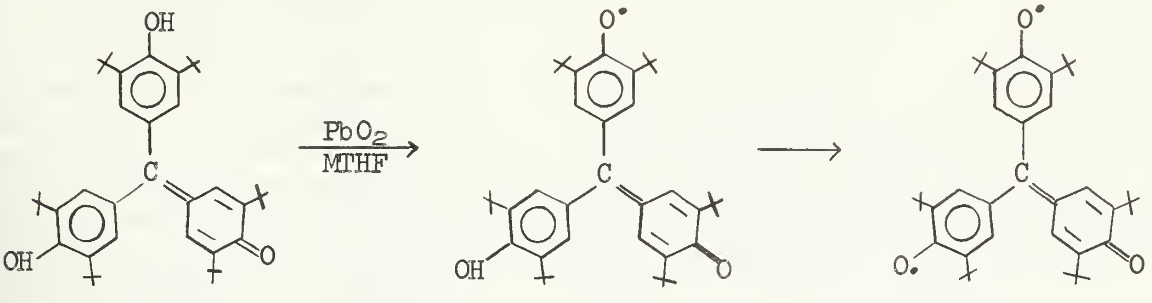
A pyridinyl diradical has been prepared and examined by Kosower and Ikegami.[13] Their esr studies of 1,1' ethylene-bis-(4-carbomethoxypyridinyl) (XVIII) indicates radical-radical association producing dimers or polymers. The ends of the n-mers behave like monoradicals as in the case of Chichibabin's hydrocarbon. The esr spectrum of XVIII at 77°K at low concentration is characteristic of a triplet with



$D = 0.0178\ cm^{-1}$ and $E = 0.0017\ cm^{-1}$. With increasing concentration, the triplet spectrum disappears as a strong signal due to the monoradical-like ends of the polymers appears. Again, it would be interesting to see whether the spin interaction here could be predicted without creating a "biradical paradox."

Young and Castro[14] prepared a stable biradical (XXI) which Kreilick[15] studied by esr. The esr spectrum at room temperature of the oxidation product of XIX initially gave an esr signal with hyperfine splitting due to four equivalent protons, from the formation of XX. On further reaction, an esr signal appeared with splitting due to six equivalent hydrogen atoms, from the formation of XXVII. Apparently, the unpaired electrons can delocalize into the three aromatic rings to interact with all six meta protons. The biradical (XXVII) esr spectrum consists of two pairs of lines disposed about g=2. The separation of the inner more intense lines is 38.4 gauss.

Since $D \propto 1/r^3$ where r is the average distance between the two unpaired electrons and the proportionality constant is known from theory,[1] a separation of 9 Å between the two unpaired electrons is calculated. The degree of spin interaction here is less than observed for XV.



XIX XX XXI

METHYLENE DERIVATIVES

The first methylene compound to be studied by esr was diphenylmethylene. Murray, Trozzolo, Wasserman, and Yager[16,17] irradiated a solution of diphenyldiazomethane in "Flororolube" (polychlorotrifluoroethylene) at 77°K with an Hg arc. The esr spectrum consisted of derivative signals at 1227, 1619, 4588, 5272, and 7522 gauss. The intensity of the spectrum did not decrease as long as the temperature was kept below 123°K, indicating the paramagnetic species was the ground-state or was at least in thermal equilibrium with the singlet-state. The five line spectrum corresponded to a triplet esr spectrum of randomly oriented molecules having a spin Hamiltonian with $D = 0.401\ \text{cm}^{-1}$ and $E = 0.018\ \text{cm}^{-1}$.

Brandon, et al.[18] subsequently presented the results of a detailed study of the esr spectra of ground-state triplet diphenylene molecules oriented in benzophenone single crystals. A preliminary examination of the esr spectra revealed that there were four differently oriented sets of principle axes indicating four equivalent but differently oriented positions in the benzophenone unit cell could be occupied by the triplet species. The major magnetic axes of the triplets in one of these equivalent sites were determined. If the magnetic field were made parallel to one of these axes and the crystal was rotated about this axis, the esr line positions at several fixed angles of rotation were measured. The variation of the magnetic field strengths necessary for resonance with respect to the angle of rotation is simulated in Fig. 3. The angles of rotation where maximum separations occur indicate the positions of the other two axes. The principle magnetic axes were determined relative to the crystallographic axes of the benzophenone single crystal. The measurements of the stationary magnetic field strengths necessary for resonance versus the angle of the external magnetic field in the plane of the principle magnetic axes were fitted by the spin Hamiltonian $\mathcal{H} = \vec{H}\cdot g\cdot(\beta)\vec{S} + D(S_z^2 - 1/3S^2) + E(S_x^2 - S_y^2)$. Those values of D and E which gave the best fit are $0.4050\ \text{cm}^{-1}$ and $0.0192\ \text{cm}^{-1}$, respectively.

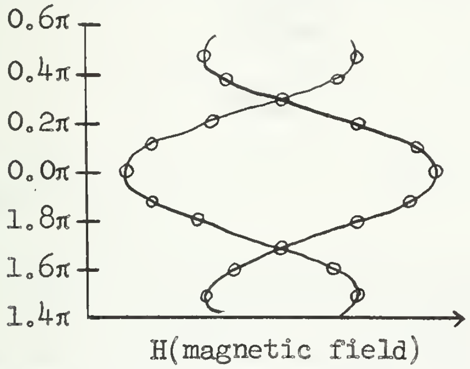
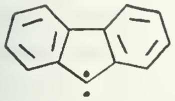


Figure 3. Variation of Triplet Line Position with Rotation about a Magnetic Axis. (The points are determined from separate esr spectra and curves are drawn to fit them.)

The zero-field splitting parameter (D) is very large compared to diradicals ($D \sim 0.01\ \text{cm}^{-1}$) and π-electron triplets ($D \sim 0.20\ \text{cm}^{-1}$). Since $D \propto 1/r^3$, the large value of D indicates the electrons in the diphenylmethylene are on the same carbon atom a large fraction of the time. Higuchi[19] has calculated the value of D for CH_2, methylene, where the two unpaired electrons are each in one of two orthogonal p orbitals,

to be 0.9055 cm^{-1}. The D value of diphenylene is smaller than D_{CH_2} indicating the unpaired electrons can delocalize into the phenyl rings. Skell[20] has proposed a linear structure for diphenylmethylene with D_{2d} symmetry, with each orthogonal p orbital conjugated with a phenyl ring. If the triplet were linear the zero-field splitting parameter E would be zero, but this is not observed. Hence, the diphenylmethylene molecule is bent. The structure of diphenylmethylene probably has one electron generally localized at the divalent carbon and the other conjugated with the phenyl rings. This bent structure for methylene compounds has been confirmed by the observation of geometric isomers of 1- and 2-naphthylmethylenes by esr.[21] The esr spectra indicated the presence of two sets of triplet species whose zero-field splitting parameters are similar indicating similar species and the difference between the zero-field splitting parameters of each isomer does not vary as the host (the frozen matrix) is changed.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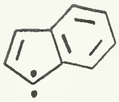
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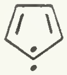
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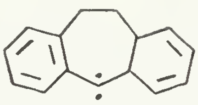
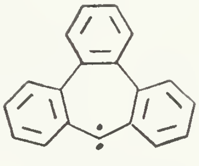
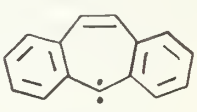

XXV


XXVI


XXVII

The zero field splitting parameters for many methylene compounds have been determined.[17,18,21-26] The D (0.518 cm^{-1}) value of phenylmethylene is larger than the D of diphenylmethylene as expected since two phenyl groups would allow greater delocalization of electrons, lowering D. The compounds XXII-XXVII have D values (0.37-0.42 cm^{-1}) similar to that of diphenylmethylene indicating a similar electronic structure (i.e. one electron localized at the divalent carbon atom and one delocalized). Propargylene derivatives[26] have relatively large values of D (0.55-0.63 cm^{-1}, but one would expect that the unpaired electrons could be delocalized into the triple bond. These compounds also have $E \simeq 0$ indicating a linear geometry at the methylene group. If the unpaired electrons delocalize, they would go into two perpendicular π systems (see Fig. 4). Then, each carbon atom of the conjugated chain would have some fraction of triplet methylene character according to the spin density of the π-system at the carbon atom. Thus, the effect of delocalization of the unpaired electrons to lower D is nulified. Theoretical calculation indicate that negative spin densities must be used to predict the experimental value of D.

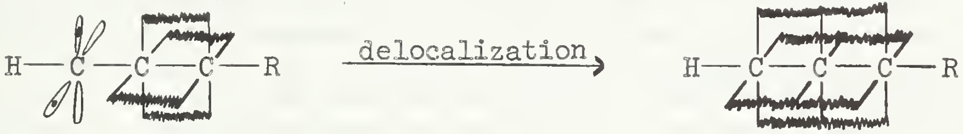
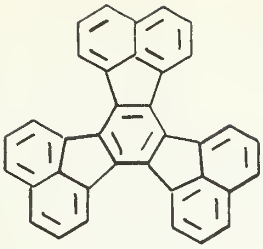


Figure 4. Delocalization of Unpaired Electrons in Propargylene (H-$\ddot{C}$-C≡CH) Derivatives

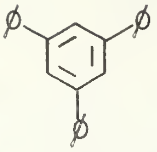
π-ELECTRON TRIPLETS

The possibility that certain derivatives of cyclic 4n π-electron systems could have triplet ground states is suggested by simple molecular orbital theory. This is based on the degeneracy of the highest occupied molecular orbitals. These orbitals are degenerate only if the system is symmetrical. If the symmetrical system is distorted (Jahn-Teller effect), the degeneracy of the orbitals is lost. If two electron are placed in the degenerate orbitals, a ground-state triplet results, but if the orbitals are not degenerate both electrons may occupy the lowest orbital giving a singlet.

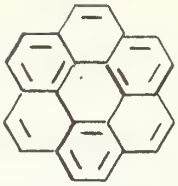
Cyclic aromatic compounds with three fold or greater axes of rotation, have two degenerate unfilled lowest anti-bonding π-electronic levels. If dinegative anions were made from the addition of two electrons to anti-bonding orbitals, they could be triplet states. Jahn-Teller effects could remove the degeneracy to allow the two electrons to occupy one orbital and form a singlet ground-state. The simplest case, benzene dinegative ion, has not been reported. However, the esr spectra of the dinegative ions of triphenylbenzene[27] (XXIX), decacylene[27] (XXVIII), and coronene[28] (XXX) have been reported. The coronene dinegative ion did not give a very intense esr spectrum in solution, but if the di-potassium coronene salt is crystallized from tetrahydrofuran, the solid obtained gives a triplet esr spectrum whose signal



XXVIII



XXIX



XXX

intensity varies intensively with temperature. At -160°C no triplet signal was observed. Increase in temperature resulted in a continuous increase of esr triplet signal intensity up to +60°C where the sample decomposed. This temperature dependence indicates a thermally excited triplet-state. The zero-field splitting parameters (D) for (XXVIII), (XXIX), and (XXX) were respectively 0.021 cm^{-1}, 0.042 cm^{-1}, and 0.052 ~~0.060~~ cm^{-1}. Since $D \propto 1/r^3$, the magnitude of D should vary inversely with the size of the π-electronic level the unpaired electrons occupy, and it does.

Cyclopentadienyl cations, which may have triplet ground-states according to simple molecular orbital theory, have been studied by esr.[29] Penta-β-naphthyl cyclopentadienyl cation did not show a triplet esr spectrum at any temperature. The pentaphenyl and pentachloro derivatives gave very distinct triplet esr spectra. If the molecule has a triplet ground-state and the excited singlet state is not appreciably populated, or the singlet and triplet states are equal in energy, the intensity of the esr spectrum should follow Curies law (i.e. intensity is inversely proportional to temperature). If the triplet is not the ground-state, the intensity of the esr signal due to the triplet still obeys Curie's law, but the concentration of the triplet varies with temperature being a thermally excited state, and thus Curie's law is not obeyed. The esr spectrum of the pentaphenylcyclopentadienyl cation did not obey Curie's law and the triplet is a thermally excited state, but the esr spectrum of the pentachlorocyclopentadienyl cation did obey Curie's law and the triplet is the ground-state or very close to it. The symmetry of the cyclopentadienyl ring would be expected to be distorted more the larger its substituents become. The more distorted the ring is the more likely the ground-state will be a singlet, and it is observed as the substituents (β-naphthyl> phenyl> chloro) on the cyclopentadienyl ring become more bulky the triplet is less stable. The zero-field splitting parameters for the pentachloro and pentaphenyl derivatives were D = 0.1495 cm^{-1} and D = 0.1050 cm^{-1}, respectively, as would be expected since the pentaphenyl derivative would allow the two unpaired electrons to have a greater average distance between them than in the pentachloro derivative.

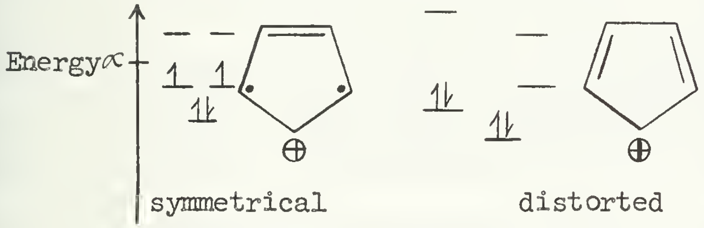


Figure 5. Energy Level Diagrams for Symmetrical and Distorted Cyclopentadienyl Cation

CONCLUSION

Many examples of triplet-state species have been presented which can be observed by esr spectroscopy. The zero-field splitting parameters can be used to infer information about the electronic structure of the triplet species. By use of esr to study reaction mixtures, it should be possible in some case to detect and characterize triplet reaction intermediates.

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RECENT STUDIES CONCERNING THE MECHANISM OF THE FAVORSKII REARRANGEMENT

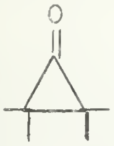
Reported by Peter A. Gebauer April 20, 1967

I. Introduction

The Favorskii rearrangement of α-haloketones to derivatives of carboxylic acids by the action of bases has been reviewed.[1,2,3,4] A general review of reactions of α-haloketones with bases has also appeared.[5] The purpose of this seminar will be to present the recent work related to the mechanism of the Favorskii rearrangement, especially that concerning the question of whether a cyclopropanone intermediate, if formed, is generated via an intermediate zwitterion or delocalized species, or whether it is formed in a concerted manner.

II. Historical

The labeling experiments by Loftfield which indicated that the α and α' carbon atoms of 2-chlorocyclohexanone become equivalent during the course of the Favorskii rearrangement limit the possibilities for the mechanism of the Favorskii rearrangement. Although one case will be discussed in which the α and α' carbons do not become equivalent, it appears that generally the reaction must proceed through either a cyclopropanone (I), or through a planar species (II)[7,8] which is probably best described as a diradical, but in keeping with the usage of most of the workers in this field, this mechanism will be referred to as the zwitterionic mechanism. Usually the intermediate (II) is considered to form a cyclopropanone in the course of the rearrangement.[8]



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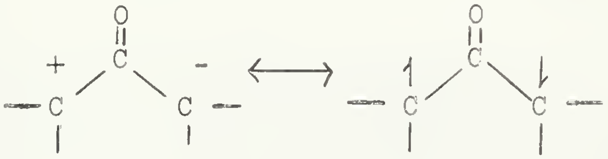


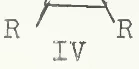
II

Burr and Dewar[8] argued against the concerted formation of the cyclopropanone on the grounds that the geometry of the p orbital on the carbanion is not correct for nucleophilic displacement of the halogen.

III. Reactions of Cyclopropanones

Breslow and co-workers[9] have reported the interception of a cyclopropanone under conditions similar to those of the Favorskii rearrangement. Cyclopropenones such as IV were obtained by treatment of the dibromides III, V, and VI with triethylamine in methylene chloride or chloroform.

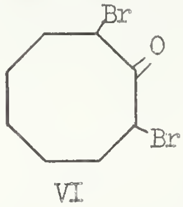
RCHBr-CO-CHBrR $\xrightarrow{Et_3N}$



IV

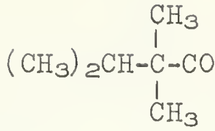
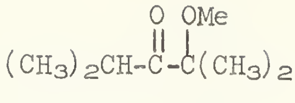
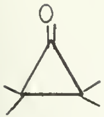
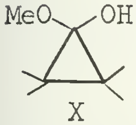
III R=Φ

V R=n-C_4H_9



VI

Turro and Hammond[10] found that cyclopropanones will react to form products analogous to those of the Favorskii rearrangement. Treatment of 2,4-dimethyl-2-bromo-3-pentanone (VII) with sodium methoxide in ether produced only 12% of the rearrangement product VIII while tetramethylcyclopropanone, IX, the expected intermediate in the Favorskii rearrangement of VII and the hemiketal of tetramethylcyclopropanone (X) produced 97% and >98% of VIII respectively. The hemiketal (X) in refluxing methanol also produced 24% of VIII. In all cases, XI was the only other product reported.

		 $(CH_3)_2CH-\overset{CH_3}{\underset{CH_3}{C}}-CO_2Me$ VIII	 $(CH_3)_2CH-\overset{O}{\overset{\Vert}{C}}-\overset{OMe}{C}(CH_3)_2$ XI
 IX	$\xrightarrow[\text{MeOH or DME}]{\text{NaOMe}}$	97%	3%
 X	$\xrightarrow[\text{"}]{\text{"}}$	>98%	<1%
"	$\xrightarrow{\text{MeOH(refl.)}}$	24%	76%
$(CH_3)_2CH-CO-CBr(CH_3)_2$ VII	$\xrightarrow[\text{Et}_2\text{O}]{\text{NaOMe}}$	12%	88%

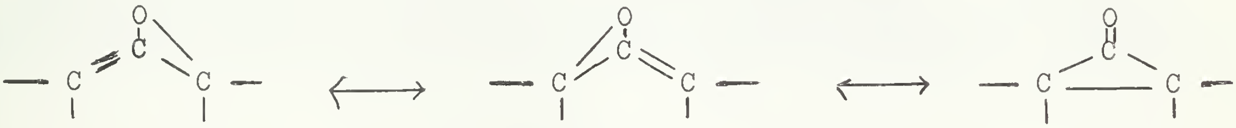
Similar results were obtained with 2,2-dimethylcyclopropanone.[11]

Turro and Hammond[10] concluded that VII does not form either the cyclopropanone or the hemiketal as the major product when treated with base. They also conclude that the cyclopropanone is in equilibrium with an acyclic species such as II. This is not necessarily required since it is possible that methanol might add directly to the cyclopropanone as suggested by House.[12]

It would seem from a comparison of the results of the reactions of the bromide in base and the hemiketal in refluxing methanol that cyclopropanones might form ketonic solvolysis products such as XI if the concentration of base were low enough. However, other means of formation of these products must, in general, be operative also.

IV. The Question of a Delocalized Intermediate

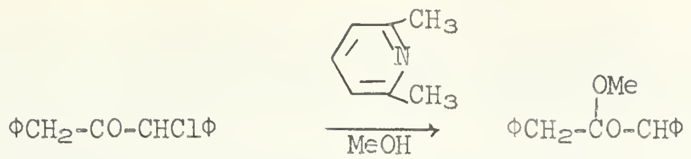
Fort[13] suggested that the intermediate (II) proposed by Aston and Newkirk[7] and Burr and Dewar[8] might not close to a cyclopropanone but react directly with solvent to form ketonic solvolysis products or with base to form rearrangement products. He suggested that XII might be the most efficient way of describing the intermediate.



XII

As indicated in XII, Fort meant to imply that there was some overlap between the radial carbons and oxygen but he conceded[14] that this would be slight due to the large distances between the radial atoms.

Fort[13] found that α-chlorodibenzyl ketone (XIII) reacted with lutidene in methanol to produce only α-methoxydibenzyl ketone (XIV). Desyl chloride (XV) and α-chloroacetone (XVI) did not react under these conditions.



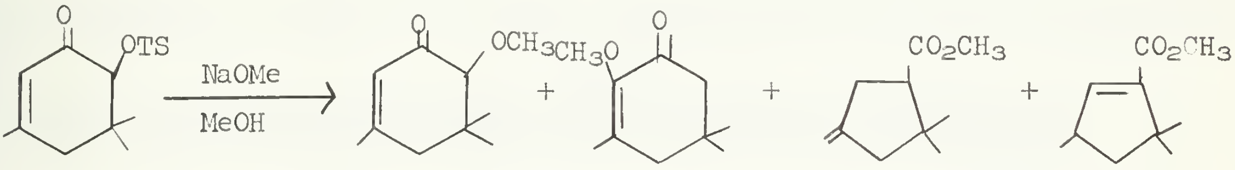
XIII XIV

Φ-CO-CHClΦ CH_3-CO-CH_2Cl

XV XVI

It was assumed that the delocalized intermediate was formed in the first case but not in the last because the base is not strong enough to form it in the absence of stabilization by phenyl groups.

Fort[14] also treated compound XVII with varying concentrations of base.



XVII XVIII XIX

He found that as the concentration of base decreased, the yields of rearrangement products also decreased, and concluded that a delocalized intermediate, which can react with base to form rearranged products (XIX) or with solvent to form ketonic solvolysis products (XVIII) was being formed.

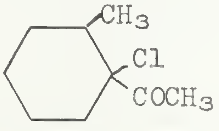
Fort's[13,14] conclusions seem to rest on the tacit assumption that a cyclopropanone would not give ketonic solvolysis products in the absence of strong base. However, as noted earlier, the work of Turro and Hammond[11,12] seems to indicate that all the reactions of the delocalized intermediate could as easily be explained by a cyclopropanone.

Fort,[15] Richey and co-workers,[16] and Cookson and co-workers[17] have trapped adducts which they all assumed were formed by the addition of an acyclic species, such as XII, to furan. Hammond and Turro[11] have also obtained a furan adduct of 2,2-dimethylcyclopropanone. Although these workers[18] suggest that the cyclopropanone may be in equilibrium with some acyclic species, it might be possible for the cyclopropanone itself to form this adduct.

V. Solvent Effects and Stereospecificity

The conflict between Loftfield's[6] concerted mechanism and the stepwise zwitterion mechanism[7,8] cannot be resolved by kinetic determinations, but the stereochemistry of the products is different for the two mechanisms.[1] Where two stereoisomeric products are possible, the concerted mechanism predicts inversion of configuration at the α carbon bearing the halogen while the zwitterion mechanism should proceed with racemization.

Stork and Borowitz[19] found that the cis and trans isomers of 1-chloro-1-acetyl-2-methylcyclohexane (XX) underwent Favorskii rearrangement with nearly complete inversion and concluded that the cyclopropanone formation was concerted.

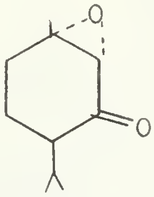


XX

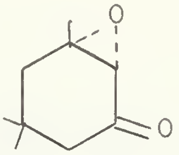
House and Gilmore[20] found, however, that the stereospecificity of the reaction seemed to depend on the polarity of the solvent. The cis isomer of XX produced essentially racemized product when the rearrangement was carried out in methanol,

and mainly inverted product in dimethoxyethane (DME). It was suggested that this solvent effect was due to polar solvents facilitating the loss of chloride to form the planar intermediate (II) while the concerted mechanism predominates in nonpolar solvents.

Similar results were obtained[21] using piperitone oxide XXI and isophorone oxide XXII as models for α-haloketones.



XXI



XXII

Tchoubar and co-workers[22,23] found a similar solvent effect with compound XX, shown in Table I.

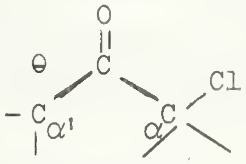
Table I

Effect of Solvent on Stereospecificity of Favorskii Rearrangement

Base	Solvent	% Inversion	% Retention
NaOMe	DMSO	75.5	24.5
(") *	(DME)	(95) *	(5)
"	t-BuOH	83.5	16.5
KOH	H_2O-Pyridine	37	63

*Values in parenthesis are from House[20] for purpose of comparison.

Tchoubar[22] argued that solvation of the anion was the factor which determined the solvent dependence. They assumed that in a nonpolar solvent the negative charge of the anion (XXIII) resides on the α' carbon which, they say, would be tetrahedral. In a polar, hydrogen bonding solvent, the solvent would be presumed to hydrogen bond with the oxygen and localize the negative charge on the oxygen atom. In this case they expected the α' carbon to be hybridized sp^2 and planar.



XXIII

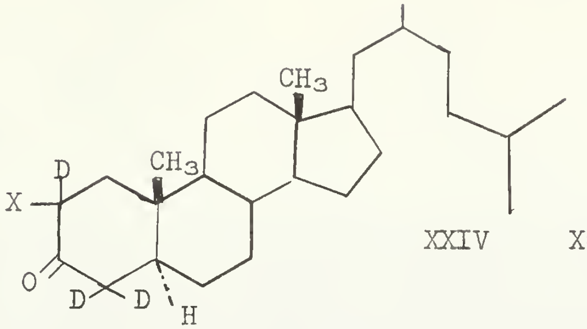
They therefore concluded that the critical difference between the suggestions of Loftfield[6] and Burr and Dewar[8] is whether the α' carbon is tetrahedral or planar.

It is unlikely that a tetrahedral carbanion would have a very long lifetime when the possibility of delocalization of the charge exists. However, the carbanion might react rapidly before rehybridization. This would require that the anion displace the chloride either very soon after, or simultaneously with, loss of the proton. This possibility can be checked by labeling studies. If the reprotonation is faster than or as fast as the loss of chloride, the anion probably has a lifetime long enough to form the more stable planar species.

House and Thompson[24] found that essentially no deuterium was incorporated into unreacted 9-chloro-trans-1-decalone when treated with sodium methoxide in deuterated methanol.

Olson[25] found that no deuterium was lost from the C-4 position in unreacted 2-α-bromo- and 2-α-iodocholestan-3-one-2,4-d_3 (XXIV), but that the corresponding chloro compound lost 20% of the label after one half life of the Favorskii rearrangement

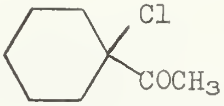
when treated with 0.2 M sodium ethoxide in absolute ethanol.



XXIV X=Cl, Br, I

Olson concluded that in the bromo- and iodo- compounds loss of a proton is rate determining while in the chloro compound, loss of chloride occurs at approximately the same rate as reprotonation. This conclusion was verified by the observation that the trideuterated compounds above lost halide at one-fifth the rate of their hydrogen analogues.

Mayer[26] and Tchoubar and co-workers[27] studied the Favorskii rearrangement of 1-acetyl-1-chlorocyclohexane (XXV), using sodium phenoxide as the base in the presence of deuterated phenol.



XXV

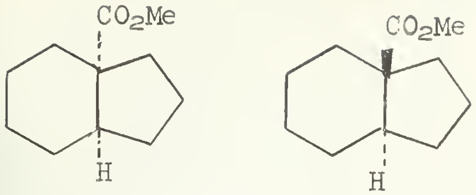
They found that about half a mole of deuterium was incorporated per mole of starting material which was recovered and concluded that the first step, at least in this case, of the Favorskii rearrangement is a pre-equilibrium between the anion and starting material. This conclusion is not necessarily valid since it is possible that the reaction which is responsible for the deuterium incorporation may not be related in any way to the Favorskii rearrangement.

House and Gilmore[21] also found deuterium incorporation in unreacted isophorone oxide and piperitone oxide.

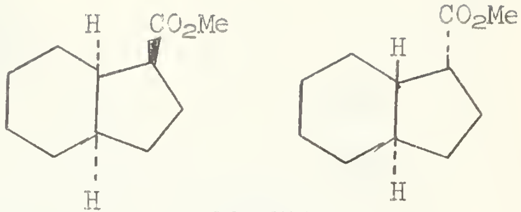
It appears that the rate of reprotonation of the anion is quite close to that of loss of halide. The anion discussed earlier therefore probably has a fairly long lifetime and is planar with the negative charge delocalized on to both the carbon and oxygen atoms.

House and Thompson[24] suggested that an equatorial halogen would favor the concerted formation of a cyclopropanone while an axial halogen should favor formation of the zwitterion or delocalized intermediate. However, work by House and Frank[12,24] using both the cis and trans isomers of 9-chloro-1-decalone (XXVI) led to the conclusion that the ketonic solvolysis products did not arise from a planar intermediate in either case since the cis and trans isomers produced different product ratios. Since the same planar intermediate should arise from both isomers, the products also should have been the same. Ketonic solvolysis products were obtained from both isomers in methanol and rearrangement products were obtained in DME. The possibility of direct nucleophilic displacement was ruled out since the 9-methoxy compounds were formed mainly with retention rather than inversion.

The trans isomer produces mainly the products (XXVII) which would be formed by the formation of the most stable carbanion, while the cis isomer produces mainly the unexpected products (XXVIII).

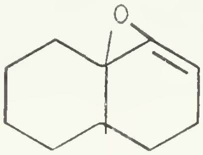


a XXVII b

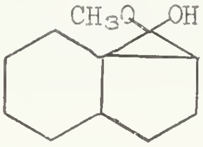


a XXVIII b

The stereochemistry at the 9-position in the 9-carbomethoxy derivatives (XXVII) was consistent with a concerted formation of the cyclopropanone. That is, the cis isomer formed XXVIIa and the trans isomer formed XXVIIb. The ketonic solvolysis products were suggested to be formed via either an alkylidine epoxide (XXIX) or the hemiketal of the cyclopropanone (XXX).



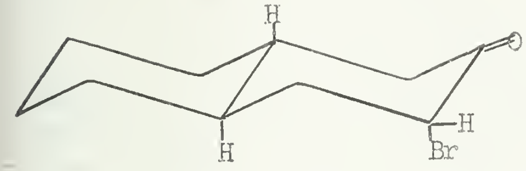
XXIX



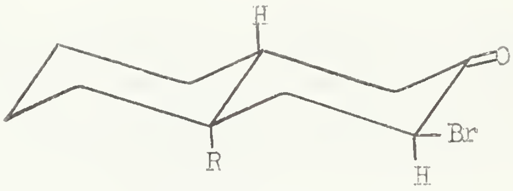
XXX

House concluded that the conformation of the halogen did not affect the mechanism of the Favorskii rearrangement.

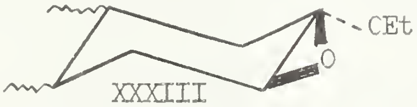
Smissman and co-workers[28] also have studied this effect. They subjected 3-a-bromo-trans-2-decalone (XXXI), 3-e-bromo-trans-2-decalone (XXXIIa) and 2-e-bromo-9-methyl-trans-3-decalone (XXXIIb) to Favorskii rearrangement conditions in polar (EtOH) and nonpolar (DME) solvents. The axial coumpound (XXXI) in both solvents produced only products which were presumed to arise from the epoxide (XXXIII). No rearrangement products were obtained.



XXXI

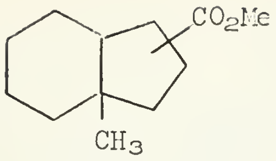


XXXII a R=H b $R=CH_3$

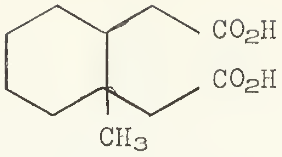


XXXIII

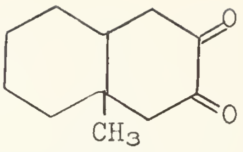
The non-methylated equatorial isomer (XXXIIa) formed both the products found in the axial case and some rearrangement product in both solvents. The methylated equatorial isomer (XXXIIb) produced 38 to 44% rearrangement product (XXXIV), a diacetic acid (XXXV) and 9-methyl-trans-decalin-2,3-dione (XXXVI). This last compound was presumed to be formed by oxidation and to be the precursor of the diacetic acid.



XXXIV



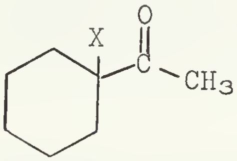
XXXV



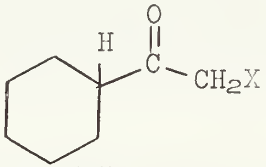
XXXVI

Rowland[29] suggests that products such as these arise from air oxidation of initially formed products, but it is unlikely that this is occurring in this case.

Smissman concluded that, in the case of the compounds which were studied, the cyclopropanone mechanism is operative, and the conformation of the halogen rather than the polarity of the solvent determined whether rearrangement will occur or not. He explains the solvent effects observed by House and Gilmore[21] by saying that the α,β-epoxyketones cannot reach a true equatorial position and so this probably effects the route of the reaction. He harks back to Wendler's[30] suggestion that halogen migration might occur before rearrangement in order to rationalize the solvent dependence in the case of 1-acetyl-1-chloro-2-methylcyclohexane.[20] Kende[1] claims that halomethyl compounds such as XXXVIII react slower than those having the halogen on a carbon in the ring as in XXXVII.



XXXVII

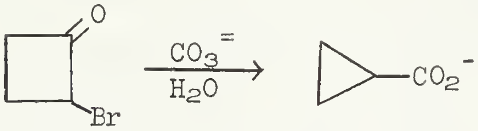


XXXVIII

If this is true, then the chlorine cannot be migrating before reaction. On the other hand House[20] says that XXXVIII qualitatively reacts faster than XXXVII, in which case no conclusion may be drawn.

VI. Rearrangement of 2-Bromocyclobutanone

The Favorskii rearrangement of 2-bromocyclobutanone (XXXIX) is known to occur under conditions, such as carbonate as the base or simply in water solution,[31] which are much milder than the usual Favorskii conditions. This fact, coupled with the fact that cyclopentanones generally do not undergo Favorskii rearrangement, seems to suggest that the mechanism which is operative in this case is not the general one for the Favorskii rearrangement.



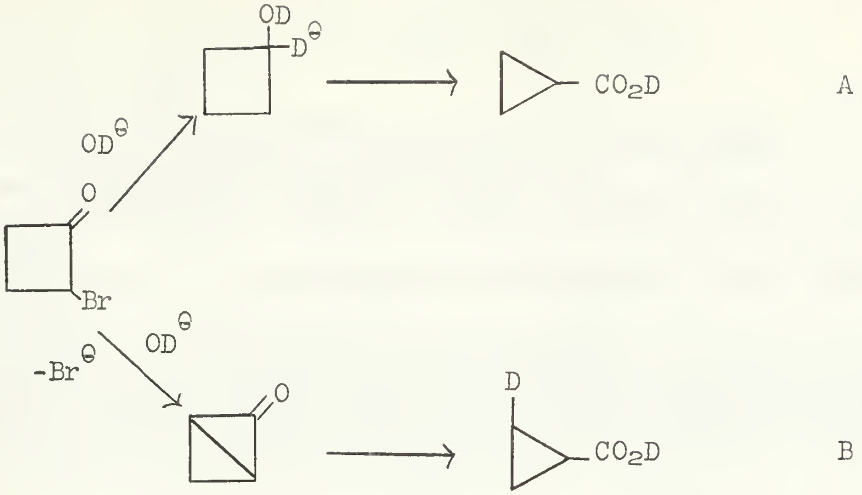
Two possible mechanisms were considered for this rearrangement:

A. Semibenzilic

B. Cyclopropanone

The predicted labeling results for these two mechanisms when run in D_2O are shown in Fig. 1.

Figure 1



The labeling studies[32] indicate that the semibenzilic mechanism is operative since no deuterium is incorporated into the ring. It has previously been shown[1,6] that this mechanism is not the general one for the Favorskii rearrangement since this mechanism is unsymmetrical. However, the rearrangement of XXXIX does indicate that, although the cyclopropanone mechanism is generally the predominating one, other mechanisms are operative in cases where the formation of a cyclopropanone is unfavorable or where the other mechanisms are particularly favored.

Conclusion

The Favorskii rearrangement appears usually to go through a cyclopropanone intermediate, although other intermediates cannot be strictly ruled out. Other points concerning this mechanism such as solvent effects and the relationship of the conformation of the halogen to the course of the reaction, appear to depend to a great extent on the system under consideration.

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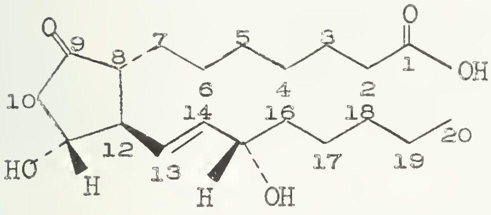
PROSTAGLANDIN SYNTHESES

Reported by Edward Bertram April 24, 1967

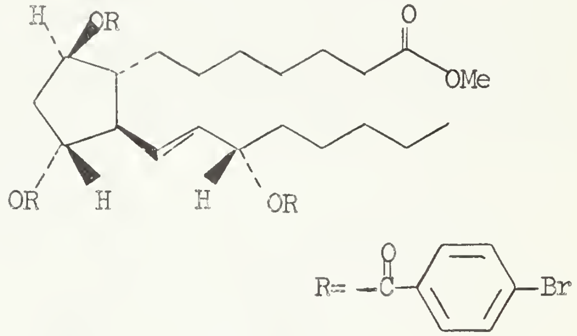
Prostaglandins are C_{20} carboxylic acids with hormone-like qualities. They show varying pharmacological effects[1] such as smooth muscle activation, lowering or raising of blood pressure, mobilization of lipids and affecting the reproductive tract. They are found in almost all parts of the body, but mainly in the vesicular glands of man and animals. This seminar will deal with their recent laboratory syntheses and the proposed mechanisms for biosynthesis.

The initial structure determination was carried out by Samuelsson and Bergstrom.[2,3] By the utilization of mass spectra, infrared, ultraviolet, optical rotation and chemical degradation, they proposed the mirror image of I as the absolute stereochemistry of prostaglandin E_1 (PGE_1). This structure was basically confirmed by Abrahamsson[4] by an X ray analysis of the tris-p-bromobenzoate methyl ester of prostaglandin $F_{1\beta}$ ($PGF_{1\beta}$) II.



(-)-11-α-15(s)-dihydroxy-9-oxo-13 trans prostenoic acid

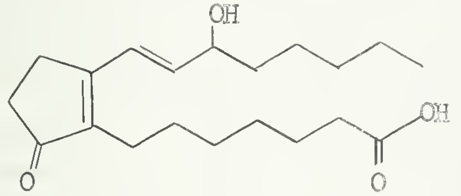
I



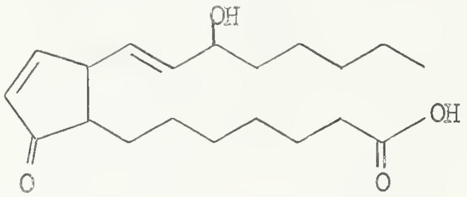
II

Since then Samuelsson, Van Dorp and co-workers[5] have re-evaluated the evidence and the determination of the optical rotations of some by-products and degradation products, and compared them to other alcohols of known absolute stereochemistry and decided that the absolute stereochemistry for PGE_1 is as shown in I.

Other prostaglandins are PGE_2 which contains an additional cis double bond at C_5 and PGE_3 which contains two additional cis double bonds at C_5 and C_{17}. The PGF_α and the PGF_β series are the prostaglandins obtained by reduction of the C_9 oxo group, β has the hydroxyl trans to the other ring hydroxyl and α contains the two hydroxyl groups cis. Other series are the PGE-217 III and PGE-278 IV. These are named after their ultraviolet spectra and are obtained as natural products or by dehydration of the C_{11} hydroxyl group. The C_{19} hydroxyl compounds of some of these α,β-unsaturated derivatives have also been isolated.[6]

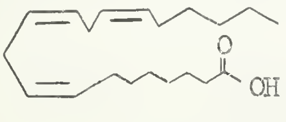


III

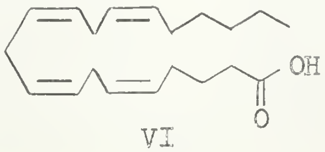


IV

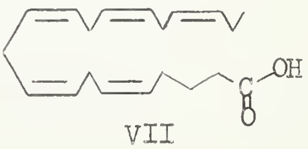
The prostaglandins are derived from essential fatty acids,[7] PGE_1 from all cis 8, 11, 14 eicosatrienoic acid V, PGE_2 from all cis 5, 8, 11, 14 eicosatetraenoic acid VI and PGE_3 from all cis 5, 8, 11, 14, 17 eicosapentaenoic acid VII. This was determined by ^3H or ^{14}C labeling studies.[8]



V



VI



VII

It was also shown that the hydrogens at C_8, C_{11} and C_{12} were not lost in the formation of PGE_1 using vesicular sheep enzyme. Klenberg and Samuelsson[9] proved this by specifically labeling the three positions with ^3H using a ^{14}C labeled 8, 11, 14 eicosatrienoic acid.

Samuelsson[10,11] and later VanDorp[12] showed conclusively that the oxygen on the ring and the C_{15} hydroxyl group came from molecular oxygen. They also proved that both the ring oxygens came from the same molecule of oxygen. Samuelsson incubated all cis 8, 11, 14 eicosatrienoic acid in an oxygen atmosphere of $^{18}O-^{18}O$ 56%, $^{16}O-^{18}O$ 1% and $^{16}O-^{16}O$ 43% and then reduced the PGE_1 to the $PGF_{1\beta}$ compound with $NaBH_4$ in EtOH, thus preventing the exchange of the keto oxygen on workup. He then methylated the hydroxyl groups and cleaved the double bond using $KMnO_4$ and periodate to obtain the diacid which he then ethylated. The mass spectrum of this compound was run and the P + 2 and the P + 4 peaks were compared for ions which still contained both oxygens. It was determined that if both oxygens in the ring resulted from the same oxygen molecule then the ratio P + 2/P + 4 would be 0.02, but if two oxygen molecules were involved then the ratio would be 1.5. He obtained a ratio of 0.06 and so concluded that both ring oxygens must be from the same molecule. VanDorp[12] used an oxygen mixture of $^{18}O-^{18}O$ 47%, $^{16}O-^{18}O$ 6% and $^{16}O-^{16}O$ 47% and a much cleaner enzyme preparation (hardly any endogenous PGE_1 present) and treated the sample in three different ways, (A) kept all original oxygens (B) exchanged the C_9 oxo group for all ^{16}O and (C) removed the oxygen at C_{15} by oxidation. He obtained the following table of values.

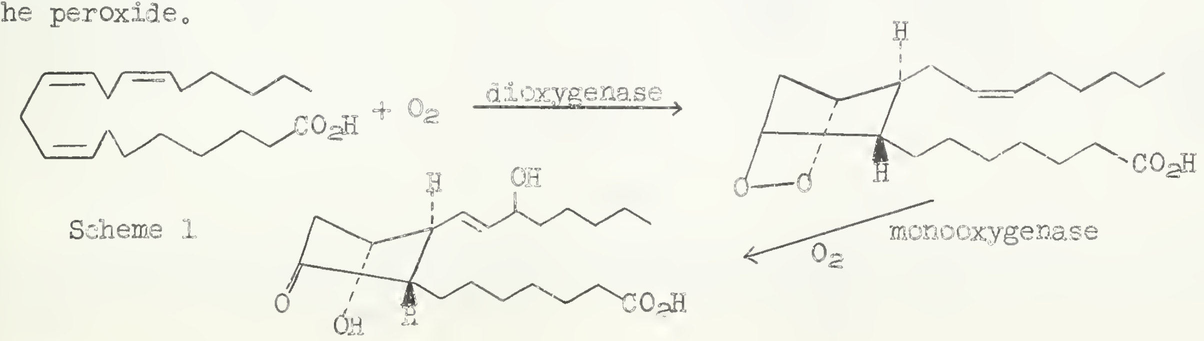
% of molecules with ^{18}O

	no ^{18}O	one ^{18}O	two ^{18}O	three ^{18}O
(A)	21%	25.5%	25.5%	28%
(B)	24%	48%	28%	0%
(C)	46%	6%	48%	0%

These experiments show that all of the oxygen functions are obtained from molecular oxygen and that both ring oxygens are from the same molecule. Van Dorp also measured the up-take of oxygen and estimated that two moles of oxygen were consumed per mole of PGE_1 formed. He also determined that Glutathione was a co-factor (almost exclusively) and that there was a need for an anti-oxidant (propyl gallate or p-hydroquinone) to obtain maximum yields of PGE_1.

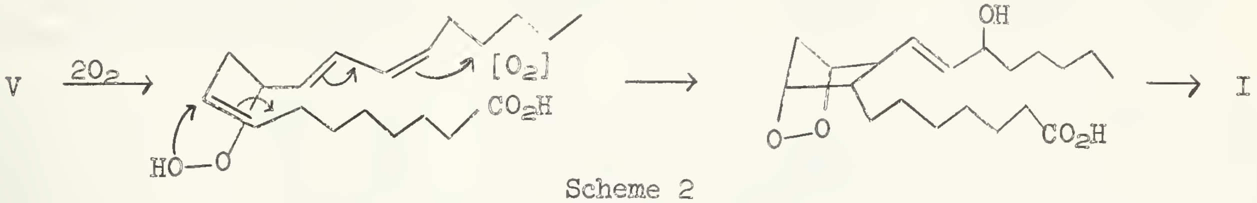
The Van Dorp group also identified several by-products obtained by varying the reagents of incubation. In a normal reaction using Glutathione and an anti-oxidant, they obtained PGE_1 I and compound VIII (11-hydroxy-8-trans-10-trans-14-cis-eicosatrienoic acid). If the anti-oxidant was left out, I, VIII, IX (11-α-hydroxy-9,15-dioxo-13prostenoic acid) and X (15-hydroperoxy-11-α-hydroxy-9-oxo-13-prostenoic acid) resulted. If Glutathione was not added, there was a significant drop in PGE_1 formation and compounds XI (12-hydroxy-8-trans-10-trans-heptadecadienoic acid), XII (9-α-15-dihydroxy-11-oxo-13-prostenoic acid) and XIII $PGF_{1\alpha}$ were isolated.

From the labeling experiments Samuelsson proposed two possible mechanisms, one (Scheme 1) was the direct molecular oxygen addition across the C_{11}, C_9 position and a conrotatory C_8, C_{12} bond formation. This would be done by a dioxygenase, a subsequent monooxygenase for the addition of a second oxygen at C_{15} followed by isomerization of the double bond to the C_{13} trans configuration and then opening of the peroxide.



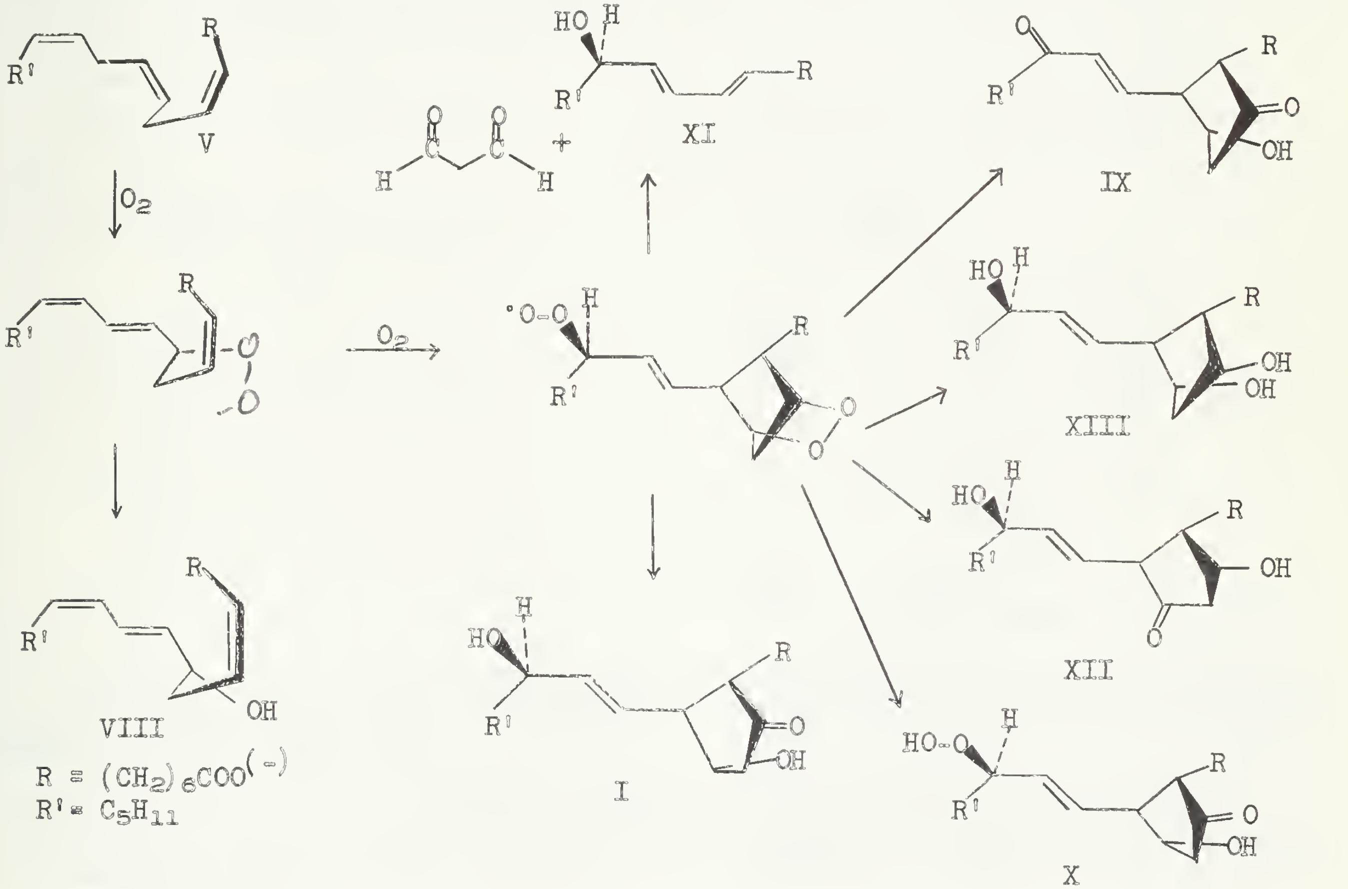
Scheme 1

A second mechanism (Scheme 2) he proposed was the formation of a hydroperoxide at C_{11}, isomerization of the double bond from Δ^{11} to Δ^{12}, then attack on the C_9 by the hydroperoxide to form a cyclic peroxide followed by a concerted ring closure to form the C_8, C_{12} bond with isomerization of the Δ^{12} bond to *trans* Δ^{13}, then the addition of a hydroxyl group at C_{15} and opening of the peroxide to give PGE_1. With only the use of the labeling experiment, Samuelsson could not determine if initial oxygenation was at C_{11}, C_9, or C_{15}.



Scheme 2

Van Dorp's proposed mechanism (Scheme 3) is similar to Scheme 2 except that he uses a peroxide radical and supports the C_{11} attack with the fact that compound VIII is formed, but no compounds have been isolated with only the C_{15} hydroxyl group or C_9 hydroxyl group. He supports the radical mechanism because of an esr band which forms when the enzyme and substrate are added and slowly disappears on incubation. He also shows that compound XI is formed from an intermediate in the PGE_1 synthesis since he has isolated a mole to mole ratio of XI and malonic aldehyde, the latter being trapped by a thiobarbituric reaction. He suggests that since no intermediates are obtained when the normal reaction is run, the process is of a concerted nature and all of it takes place while the substrate is attached to the enzyme. Also, none of the products isolated could be transformed into PGE_1 on further incubation.



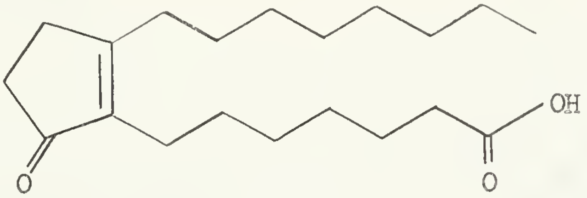
$R = (CH_2)_6COO^{(-)}$
$R' = C_5H_{11}$

Scheme 3

The esr data favor the peroxide radical, but they do not rule out the hydroperoxide since the esr band may be due to other sources. The initial attack at C_{11} seems to be favored by the isolation of VIII, in slight contrast to the fact that the

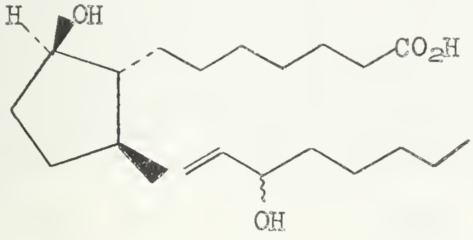
ω6 double bond compounds (double bond 6 carbons from the CH_3 end of the chain) are the most specific for the enzyme.[13] A free carboxyl group is also required[14] and a C_{20} fatty acid is favored over C_{18}, C_{19}, C_{21} or C_{22} fatty acids.[15,16] A systematic substrate specificity search has not yet been done. There has been extensive work done on inhibitors and co-factors by Van Dorp and co-workers.[12]

A simple synthesis of the prostaglandin structure was used in the structural determination by Samuelsson and Stallberg.[17] They succeeded in synthesizing XIV by two methods using Grignard and condensation type reactions. No report on the biological activity was given.

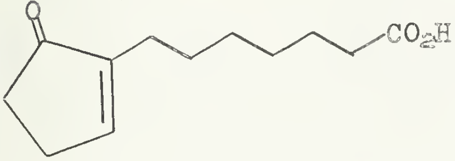


XIV

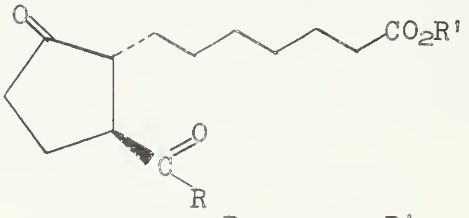
Since then there have been several syntheses reported. Bagli[18] and co-workers have succeeded in making XV, a derivative of PGE_1. They started with the potassium salt of ethyl 2-cyclopentanone carboxylate and alkylated it using 7-bromoethylheptanoate. It was then monobrominated and after refluxing the monobromo derivative in 20% H_2SO_4 XVI resulted. On reaction of XVI with acetone cyanhydrin in $NaCO_3$ and $H_2O/MeOH$, a nitrile was obtained which yielded the trans carboxylic acid XVII on hydrolysis. A monoesterification to XVIII was then accomplished by refluxing with a 0.5 mole excess of p-toluenesulfonic acid in MeOH for 55 minutes. This ester was transformed to the acid chloride XIX and the acid chloride was reacted with acetylene in the presence of $AlCl_3$ in CCl_4 to form a vinyl chloride XX which yielded the methyl ketal XXI on basic hydrolysis in MeOH.

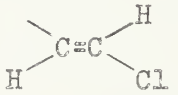
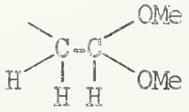


XV



XVI



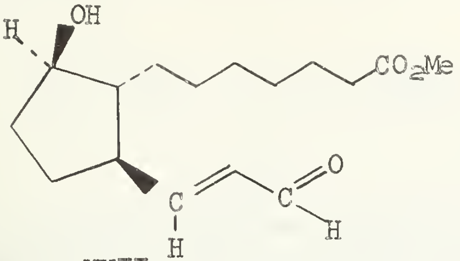
	R	R'
XVII	OH	H
XVIII	OH	Me
XIX	Cl	Me
XX		Me
XXI		Me

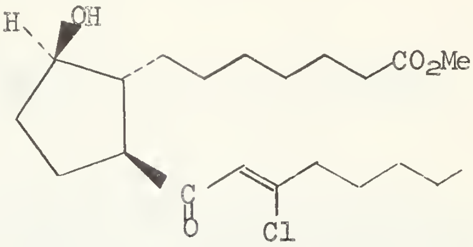
The reaction of XXI with $NaBH_4$ yielded a mixture from which XXII was obtained after refluxing in 2N H_2SO_4. This compound was then reacted with n-pentyl magnesium bromide to yield compound XV.

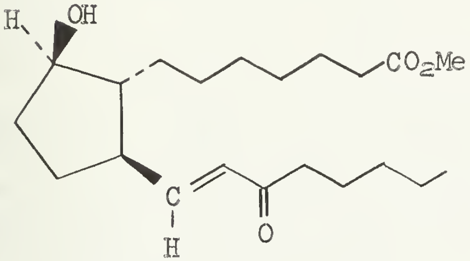
Since then the Bagli group have modified their synthesis.[19] They reacted 1-heptyne with XIX, the acid chloride, to form the vinyl chloride XXIII which was transformed by NaOH in MeOH to a vinyl methoxy compound. A $NaBH_4$ reduction followed by hydrolysis yielded a ketone XXIV which on further $NaBH_4$ reduction resulted in the formation of XV.

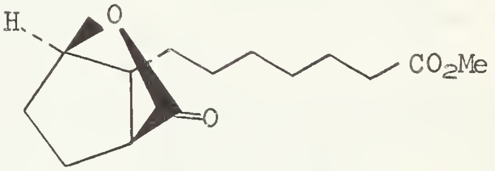
The stereochemistry of the product was shown by the reduction of XVIII with $NaBH_4$ to yield a mixture, 85% of which could be transformed into a lactone XXV. This same lactone could be formed from the product of oxidative cleavage of XV thus placing the hydroxyl and carboxyl group cis to one another.

The *trans* stereochemistry of the two chains was suggested by analogy to the reaction in which only the *trans* compound is obtained when *cis* 2,3 dialkyl cyclopentanone is refluxed in base, as was XVII when it was formed from the nitrile.


XXII

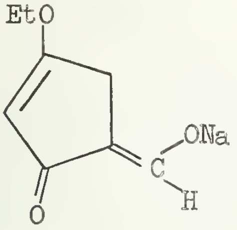

XXIII

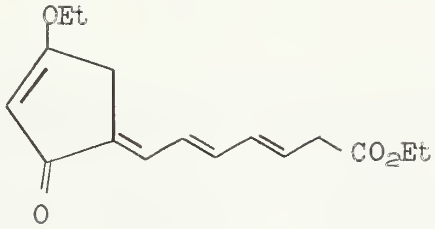

XXIV

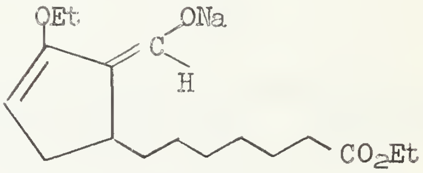

XXV

The compound that was synthesized (XV) has not yet been identified as a natural product, but it still possesses a vaso depressor effect, which is amazing in view of the lack of oxygen at the C_{11} poistion. A method for adding this C_{11} oxygen function has been reported by Bagli,[20] but no details are available.

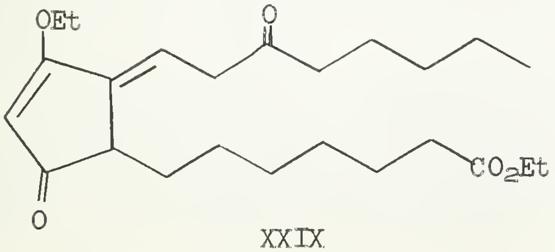
The first total synthesis of a naturally occurring prostaglandin has been accomplished by Beal and co-workers[22] who succeeded in synthesizing the dihydro PGE_1 XXXII which is a metabolite present after the incubation of PGE_1 in pig lung enzyme preparation.[21] Beginning with a formylation of 3-ethoxy-2-cyclopentenone, they obtained almost a quantitative yield of the sodium salt XXVI. This compound then underwent an in-situ Wittig reaction to give compound XXVII which on catalytic reduction and a second formylation gave the sodium salt XXVIII.

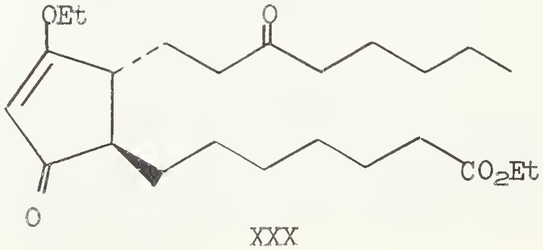

XXVI

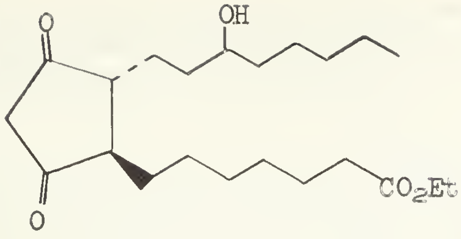

XXVII


XXVIII

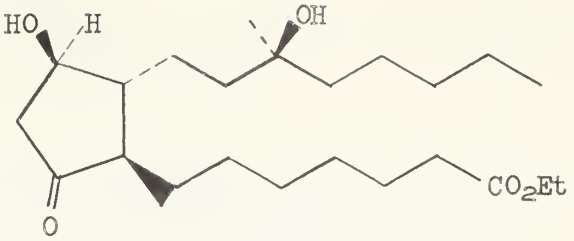
This sodium salt was then put through a second modified Wittig reaction using n-hexanoylmethylenetriphenylphosphonium chloride and gave XXIX which on catalytic reduction resulted in 85% XXX. Acid catalyzed solvolysis of XXX in benzyl alcohol resulted in the corresponding benzyl enol ether. The ketone was reduced to the 15 hydroxy compound using tri-t-butyl aluminum hydride and this compound was then converted to the diketone XXXI by hydrogenolysis. XXXI was rigorously reduced using 30% rhodium on carbon to give a mixture, 11% of which corresponded by tlc to XXXII.


XXIX


XXX



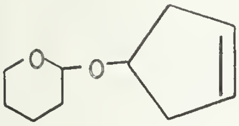
XXXI



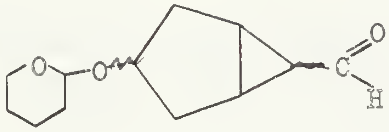
XXXII

Compound XXXII was compared with the natural dihydro PGE_1 using ultraviolet, infrared, mass spectra, nmr and tlc. It was also shown by a radio isotope dilution experiment using the NaB^3H_4 reduced product and crystalline optically active natural (biosynthetic) dihydro $PGF_{1\beta}$ methyl ester to contain at least 22% of a compound with all asymmetric centers identical to the natural compound. If the reaction had been random, it would have contained only 6% of the desired product.

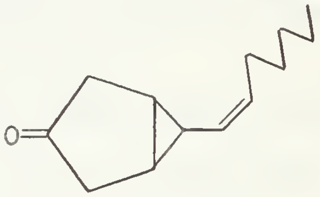
A third method of synthesis by Just and Simonovitch[23,24] has been reported in Chemistry in Canada. They oxygenated the hydroboration product from cyclopentadiene and protected the resulting cyclopenta-3-enol as the tetrahydropyranol ether XXXIII. A reaction of XXXIII with diazoacetic ester over copper powder resulted in a mixture of exo-endo, syn-anti compounds which on refluxing in methanolic sodium methoxide resulted in an exo, syn-anti mixture. The exo compound was reduced with $LiAlH_4$ and the alcohol obtained was oxidized to the aldehyde XXXIV. The aldehyde underwent a Wittig reaction with hexyltriphenyl phosphonium bromide to yield four isomers which could be separated by tlc. Hydrolysis in refluxing 0.5% oxalic acid in methanol resulted in the alcohol which was oxidized using Jones reagent to the ketone XXXV as a mixture of cis-trans isomers. These isomers were separated by tlc, the trans having a 957 cm^{-1} band in the infrared.



XXXIII

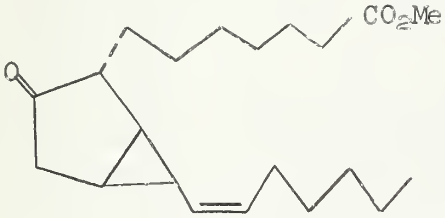


XXXIV

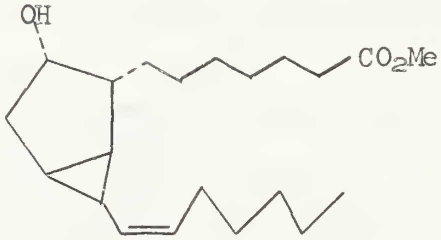


XXXV

The alkylation of XXXV was accomplished using seven equivalents of methyl-7-iodoheptanoate in dimethoxyethane and potassium t-butoxide as the base. The enamine alkylation was also attempted but gave a lower yield. The alkylation was made difficult by the problems of separation of XXXV from the product XXXVI, and the instability of compound XXXV. An effective separation was accomplished by reduction of the ketone with $NaBH_4$ to yield XXXVII.



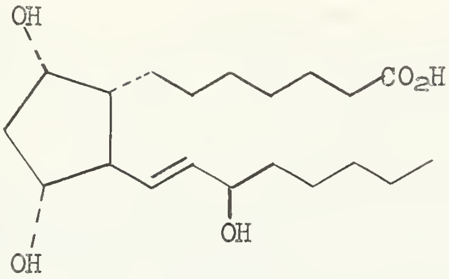
XXXVI



XXXVII

The acid obtained by NaOH hydrolysis in aqueous methanol of XXXVII was oxidatively solvolyzed using one equivalent of H_2O_2 in a Na_2CO_3 buffered solution of formic acid, followed by shaking in 10% aqueous Na_2CO_3 and resulted in dl $PGF_{1\alpha}$ XXXVIII. PGE_1 was also obtained by a similar oxidative solvolysis of XXXVI. The $PGF_{1\alpha}$ was identical by mass spectra and tlc to natural $PGF_{1\alpha}$.

Several biological tests were run and the dl $PGF_{1\alpha}$ was found to have one-half the smooth muscle activity of natural $PGF_{1\alpha}$ while the activity of the synthesized PGE_1 compound was only of the order of 10-25% of natural PGE_1.



XXXVIII

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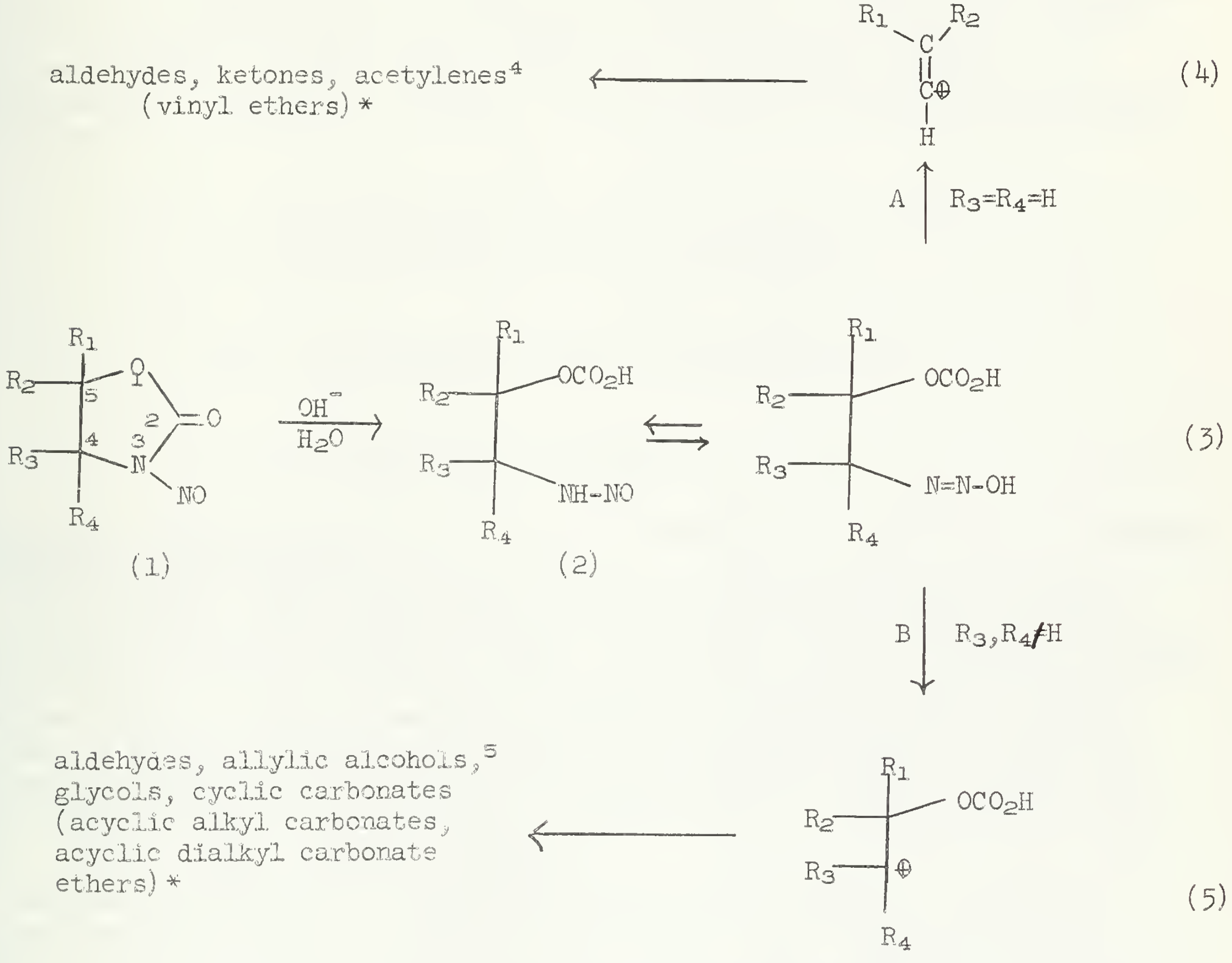
POSSIBLE VINYL CATION INTERMEDIATES

Reported by David A. Simpson May 1, 1967

Within the past few years vinyl cations have been postulated as intermediates in a variety of reactions. The textbook rule regarding the reputed instability of these ions is based primarily on the unreactivity of vinyl halides toward alcoholic silver nitrate.[1,2] Thus vinyl chloride on long heating with solutions of silver nitrate in ethanol gives no silver chloride. However, recent studies have questioned the general instability of vinyl carbonium ions. It is the purpose of this seminar to review those reactions which have been claimed to proceed through such intermediates.

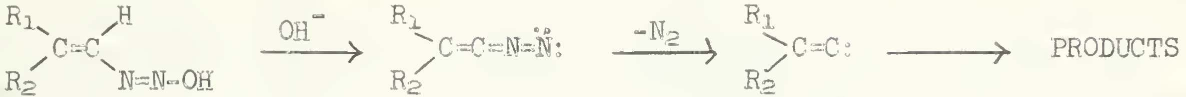
The first postulation of a vinyl cation intermediate was made in 1951 by Newman and associates as a result of studying the alkaline decomposition of 3-nitroso-2-oxazolidones (1). The following mechanism was proposed:[3]


aldehydes, ketones, acetylenes4
(vinyl ethers) *
(4)
A
R3=R4=H
OH−
H2O
(1)
(2)
(3)
B
R3,R4≠H
aldehydes, allylic alcohols,5
glycols, cyclic carbonates
(acyclic alkyl carbonates,
acyclic dialkyl carbonate
ethers) *
(5)

* reaction carried out in anhydrous alcohol using the corresponding sodium alkoxide

The first step was thought to involve ring opening of (1) to a nitrosamine (2) followed by tautomerism to an hydroxyazo intermediate (3). Two paths of reaction are now open to (3): path A involves the initial formation of an unsaturated diazonium hydroxide intermediate (by the base catalyzed elimination of carbonic acid) followed by loss of nitrogen to yield the vinyl carbonium ion (4), and then formation of products; or (3) could lose nitrogen first yielding the saturated carbonium ion (5) which then yields products. All products obtained from the 4,4-disubstituted oxazolidones could be explained by path B, but it was necessary to invoke path A to account for the products resulting from the

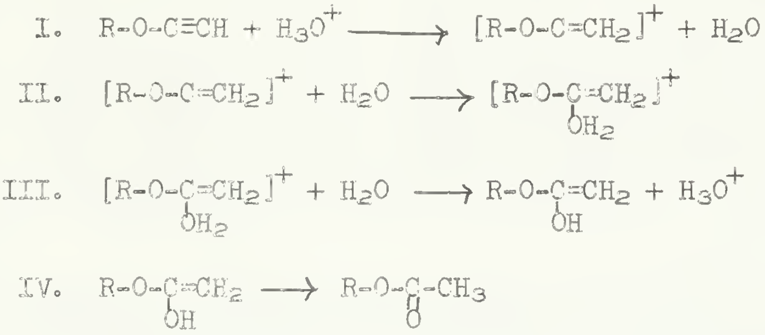
5,5-disubstituted derivatives.[5] Although path A seems to explain all the experimental observations adequately, a mechanism involving an intermediate methylene (6) cannot be rigorously excluded.[6]



(6)

At any rate, there does not seem to be enough evidence to support any of the possible mechanisms very strongly relative to the others.

Acetylene derivatives have served as the source for a number of proposed vinyl cation intermediates. The earliest example was reported by Jacobs and Searles who claimed that the hydration of acetylenic ethers appeared to be similar to that of vinyl ethers. That is, the hydration involved a rate-determining formation of a carbonium ion.[7] They measured the rates of hydration of several acetylenic ethers in alcohol-water solutions by a dilatometric method. The rates were found to be first order with respect to acetylenic ether and to hydronium ion. A mechanism consistent with the observed kinetics was formulated as follows:[8]



$$\text{I.}\quad R\text{-}O\text{-}C{\equiv}CH + H_3O^+ \longrightarrow [R\text{-}O\text{-}C{=}CH_2]^+ + H_2O$$

$$\text{II.}\quad [R\text{-}O\text{-}C{=}CH_2]^+ + H_2O \longrightarrow [R\text{-}O\text{-}\underset{\displaystyle OH_2}{\underset{|}{C}}{=}CH_2]^+$$

$$\text{III.}\quad [R\text{-}O\text{-}\underset{\displaystyle OH_2}{\underset{|}{C}}{=}CH_2]^+ + H_2O \longrightarrow R\text{-}O\text{-}\underset{\displaystyle OH}{\underset{|}{C}}{=}CH_2 + H_3O^+$$

$$\text{IV.}\quad R\text{-}O\text{-}\underset{\displaystyle OH}{\underset{|}{C}}{=}CH_2 \longrightarrow R\text{-}O\text{-}\underset{\displaystyle O}{\underset{\|}{C}}\text{-}CH_3$$

The authors believed that the first step was rate-determining and that the reaction was specific acid-catalyzed.

Sixteen years later Drenth and co-workers undertook a study of the hydration of acetylenic ethers and thioethers. Their rate studies largely confirmed the findings of Jacobs and Searles, however, the reactions were found to be general acid-catalyzed.[9,10] The observation of general acid catalysis indicated that the first step of Jacobs and Searles' mechanism was rate-determining. Most of the work of Drenth was aimed at confirming the rate-determining first step and educing the timing of the addition of the water molecule. Only the results of their investigations of the acetylenic thioethers will be summarized in this seminar. However, many of the same experiments and results were also shown to apply in studies of the acetylenic ethers.

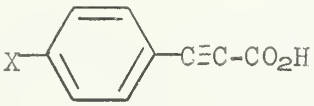
Evidence presented for a rate-determining proton transfer in the general acid-catalyzed hydration is condensed as follows: (1) the reaction is faster in H_2O than in D_2O, for ethylthioethyne the ratio of k_{D_2O}/k_{H_2O} amounts to 0.47; (2) substitution of a tertiary butyl group for the ethyl group in ethylthioethyne results in a rate enhancement.[10] If step II is rate-determining, it would be expected that the t-butyl compound would hydrate slower than the ethyl derivative, since the addition of a water molecule in II would be more sterically hindered in the case of the t-butyl derivative. The fact that the latter compound is hydrated even faster than the ethyl derivative indicates that the proton transfer must be the kinetically important step (application of the Taft equation to a series of thioethers further shows that steric effects are not essential).[11] And (3), infrared analysis of recovered ethylthioethyne from a reaction in heavy water shows that a pre-equilibrium is not important in this reaction.[12]

Since the addition of the water molecule could occur simultaneously with the proton transfer or in a subsequent step, Drenth's group set out to determine the

timing of addition. Abbreviating their findings: the activity postulate of Grunwald for reactions in alcohol-water mixtures; the relation of Zucker and Hammett; and entropy considerations all seem to indicate that a water molecule is not covalently involved in the rate-determining step of the reaction. Therefore, the authors concluded that addition of water takes place in a step subsequent to protonation.[12] The evidence presented render both a π-complex mechanism and a cyclic transition state involving the ether, hydronium ion, and water improbable. Thus, the rate-determining formation of a vinyl cation intermediate is strongly indicated.

Peterson has reported evidence for a rate-determining formation of a vinyl cation in the acid-catalyzed hydration of phenylpropiolic acids (7) and phenylacetylenes. Pseudo-first-order rate constants for the acids (7a-d) were measured

(7)

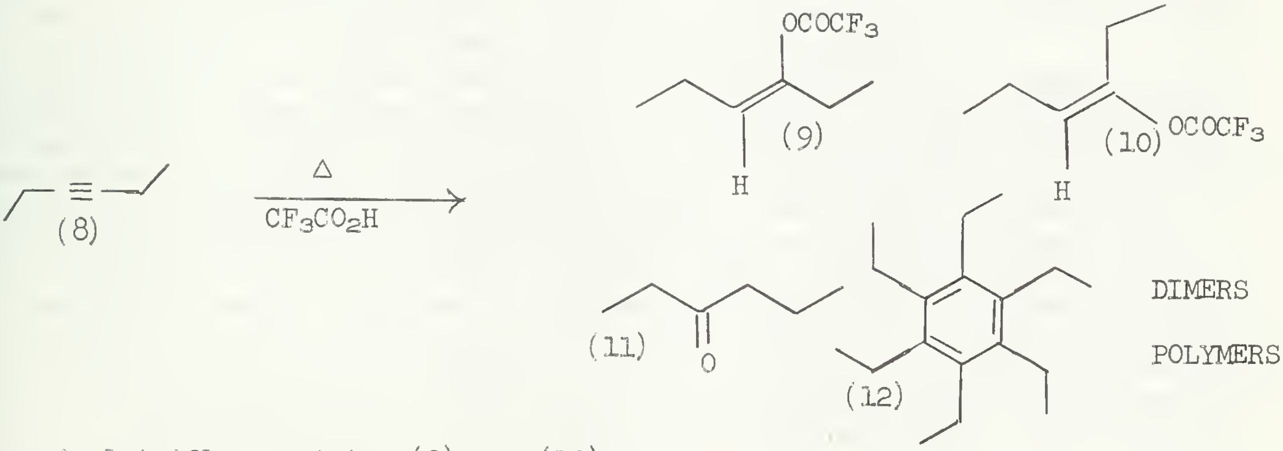


a, X=OCH_3 c, X=H

b, X=CH_3 d, X=Cl

spectrophotometrically and the rate data were found to correlate with σ^+, $\rho = -4.79 \pm 0.02$. The authors claim that the large negative value of ρ indicates a high degree of positive charge on the benzylic carbon in the transition state and therefore that the $C-OH_2$ bond formation occurs after proton transfer. In addition a solvent kinetic isotope effect implies a rate-determining proton transfer.[13] Further studies of ortho, meta, and para substituted phenylacetylenes by Bott, Eaborn, and Walton again suggest a rate-determining proton transfer. This is followed by a rapid reaction of the formed vinyl carbonium ion with solvent to form the ketone.[14]

Recently, vinyl cations have been implicated in the reactions of trifluoroacetic acid with alkynes. In a preliminary report Peterson and Duddey regarded the vinylic trifluoroacetates formed as arising from intermediate substituted vinyl cations.[15] This communication was followed by a more detailed study of the reactions of unsubstituted hexynes and 5-substituted-1-pentynes. Evidence for the cationic nature of the transition states was obtained by comparing the reactions of the substituted alkynes to the previously studied reactions of identically substituted alkenes.[16] A Hammett-Taft plot (Taft's σ_I values for trifluoroacetic acid derived from fluorine nmr frequencies)[17] showed the rate constants for the alkynes were only slightly smaller than those of the alkenes, and demonstrated nearly the same pattern of substituent effects for both, indicating similar cationic like transition states. The study of the reaction of 3-hexyne is especially interesting.



The vinyl trifluoracetates (9) and (10) were formed in nearly identical amounts and were shown to be stable under the reaction conditions. Thus, they were reported

to have arisen from nonstereospecific addition. The yields of (9), (10) and (12) were found to vary with the hexyne concentration as shown in Table I.[18]

Table I.

Molarity of 3-hexyne	(9) and (10) mole %	(12) mole %
0.107	98	2
1.03	24	21
2.00	18	30

Besides a sweeping generalization that vinyl cations are readily accessible by addition of protons to alkynes, the authors had little to say concerning the above findings. However, it is tempting to interpret the observation of nonstereospecific addition as rendering mechanisms involving a π-complex or concerted type transition state improbable for this system. The product dependence on the concentration of 3-hexyne could be rationalized by attack of the vinyl cation derived from 3-hexyne on a second molecule of substrate.

Peterson and Kamat have reported the formation of a transition state resembling a vinyl cation in the related trifluoroacetolysis of 6-heptyn-2-yl p-toluenesulfonate.[19]

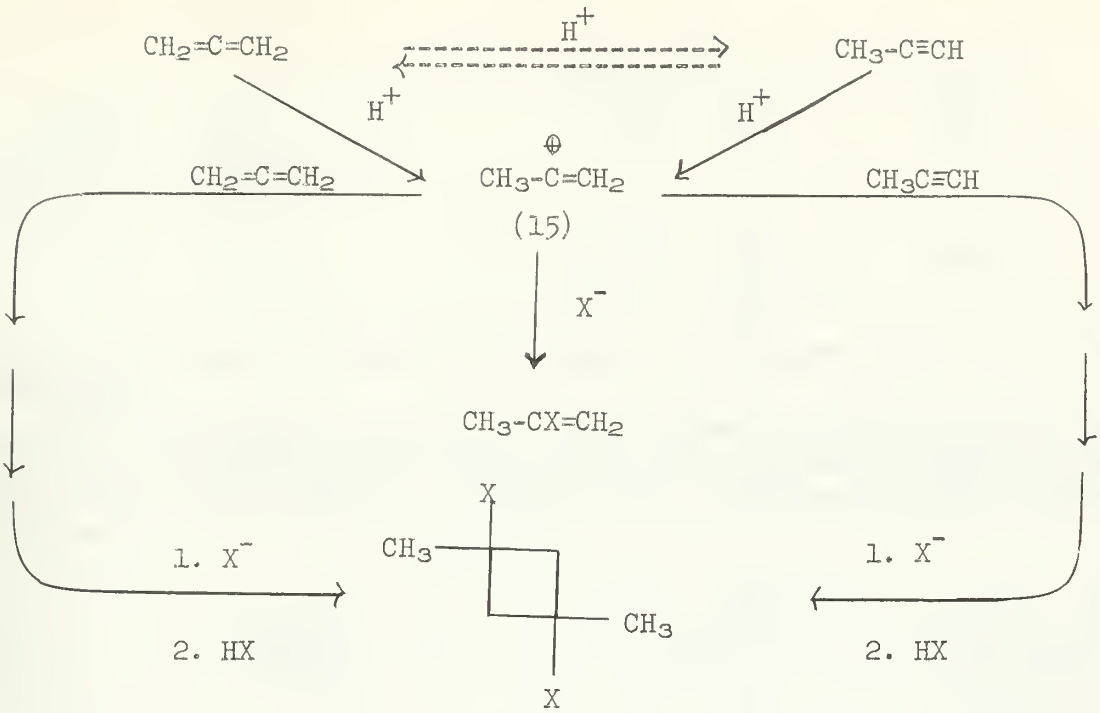
Fahey and Lee have recently studied the reaction 1-phenylpropyne with hydrogen chloride in acetic acid. The observed kinetics (reaction found to follow a third-order rate law, first-order in acetylene and second-order in hydrogen chloride) and the stereochemistry of the products lead the authors to propose a mechanism involving intimate and solvent separated vinyl carbonium-hydrogen dichloride ion pairs as intermediates.[20]

Another reaction involving protonation of an unsaturated system, which may lead to vinyl cations, is the addition of compounds of the form HX to allenes. The chemistry of allene has recently been reviewed.[21] The addition of HX to allene has been observed to follow Markovnikov's rule. For a long time it was thought that 2-substituted propenes and/or 2,2-disubstituted propanes were the only products of such additions.[22] However, Griesbaum and associates have recently

$$H_2C{=}C{=}CH_2 \xrightarrow{HX} \underset{(13)}{H_3C{-}CX{=}CH_2} + \underset{(14)}{H_3C{-}CX_2{-}CH_3}$$

found such reactions to be more complex. It was reported that in the electrophilic addition of hydrogen bromide to allene considerable amounts of 1,3-dibromo-1,3-dimethylcyclobutane (two isomers) were formed, as well as the conventional products (13) and (14).[23] Structural proof for the cyclic compounds consisted of mass spectral, nuclear magnetic resonance, and infrared data. Additional evidence was obtained by reducing the dibromo compound with tri-butyltin hydride to yield a mixture of the isomeric 1,3-dimethylcyclobutanes.

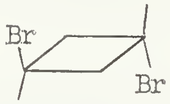
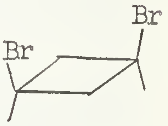
Formation of the cyclic products by a thermal reaction was considered improbable since thermal dimerization of allene leads to a 1,2-1,2 adduct, while hydrogen bromide addition causes a formal 1,2-2,1 dimerization. Reaction of 2-bromopropene (13, X=Br) with hydrogen bromide under the conditions of the allene addition led exclusively to 2,2-dibromopropane. Ultraviolet irradiation of 2-bromopropene gave essentially starting material and showed no traces of the cyclic products. Thus, the authors concluded that a simple dimerization of 2-bromopropene was not involved. Furthermore, since the free radical addition of hydrogen bromide to allene yields no cyclic products,[24] the cyclodimerization was thought to be an ionic reaction. Since the reaction of methylacetylene with hydrogen bromide also led to cyclo-dimerization,[25] and because the rearrangement of allene to methylacetylene in the presence of hydrogen bromide could not be ruled out, the following path was proposed.[26]



While the intermediate steps in the above scheme remain unclear, the authors felt that the vinylic cation (15) was involved in the cyclizations. Some data for the addition of hydrogen bromide to allene and methylacetylene is reported in Table II.

Table II.[26]

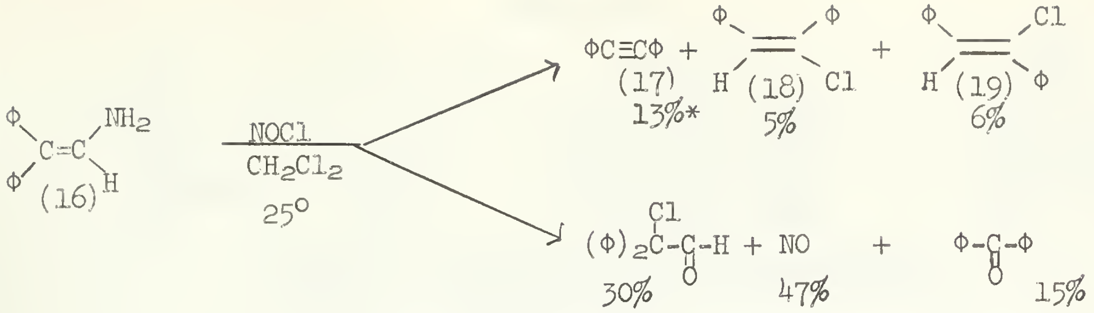
Relative amounts of components in adduct mixture, wt. %

	Substrate	$BrCH=CHCH_3$	$CH_3CBr=CH_2$	$CH_3CBr_2CH_3$		
Run #1	$CH_3C\equiv CH$	30	17	24	23	6
	$CH_2=C=CH_2$		24	34	33	9
Run #2*	$CH_3C\equiv CH$	6	56	25	9	3
	$CH_2=C=CH_2$		60	27	10	3

* run #2 contained hydroquinone as inhibitor

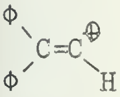
Evidence that the 1-bromopropene is formed by a concurrent free radical addition is shown by the effect of the inhibitor on its yield. If one ignores the free radical addition product, the methylacetylene and allene additions show the same selectivity for the remaining products. It should be mentioned that the determination of product yields in Table II is not completely clear. The authors claim that the components comprised 75-98% of the total adduct mixtures (depending on the purity of the starting materials). However, it was not indicated how this estimate was made (no mention of internal standard use). Accordingly these values may not be too reliable. Furthermore, a mechanism involving concerted addition cannot be rigidly excluded.

A possible route to a vinyl cation could be deamination of vinyl amines. Curtin's group has examined several such deaminations. The reaction of 2,2-diphenylvinylamine (16) with nitrosyl chloride is especially relevant to this discussion.[27] The formation of (17), (18) and (19) was explained in terms of a



* amounts of products obtained are reported as mole per cent based on amine employed

carbonium ion rearrangement from the ion (20), formed by loss of nitrogen from the diazonium ion, to the ion (21). The ion (21) could lose a proton to form the acetylene (17) or suffer attack by chloride ion to give the cis- (18) and trans- (19) chlorides.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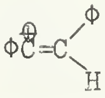
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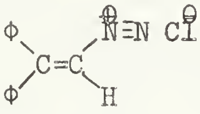
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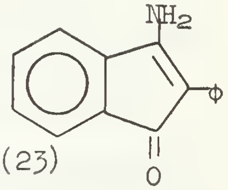
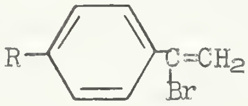

(23)

The nearly random formation of these three products is of particular interest. The authors interpret the results as being consistent with three differently oriented vinyl carbonium-chloride ion pair intermediates. The possibility of (20) fragmenting into a phenyl cation and phenyl acetylene followed by readdition was deemed improbable since gas phase chromatography of the product mixture showed no traces of phenylacetylene or chlorobenzene. The product of replacement without rearrangement, 2,2-diphenylvinylchloride,was shown to be present to a maximum of 2%.[27] However, an intermediate bridged ion could not be rigorously excluded by the authors.[28]

All attempts to intercept the diazonium intermediate (22) with the sodium salt of β-naphthol failed. It was concluded that the diphenylvinyl system did not provide the necessary stabilization of (22) and destabilization of (20) and (21) which is required for trapping. The instability of the diazonium ion was attributed to possible participation of the aromatic ring in the transition state for loss of nitrogen and/or freedom of the vinylcarbonium ion to assume sp hybridization.[29] A study of 3-amino-2-phenylindenone (23) was initiated in hopes that it would be free of these difficulties. Again attempts to intercept the diazonium intermediate failed. However, during the reaction of (23) with nitrosyl chloride at -10° an infrared absorption appeared at 2090 cm^{-1}. Observation of this peak over a period of time showed that it disappeared according to a first-order rate law. The authors stated that no definite assignment could be made to this absorption, but it might be ascribed to a diazonium or diazoalkane intermediate.[30,31]

Studies by Grob and Cseh on the solvolysis of α-bromostyrenes (24) have questioned the "well-known" general unreactivity of vinyl halides. The first-order

(24)



R= -H, $-NH_2$, $-OCH_3$, $-NHCOCH_3$, $-NO_2$

rate constants for 0.01 M solutions of these compounds in 80% ethanol with 0.01 M triethylamine were determined and appear in Table III.[32]

Table III.

(24)	temperature	k(sec^{-1})	$k_{rel}^{100^\circ}$
R= $-NH_2$	0.00	9.57(9.49)* X 10^{-5}	5.5 X 10^8
$-OCH_3$	100.10	3.60(3.60) X 10^{-5}	8.5 X 10^3
$-NHCOCH_3$	115.20	3.80(3.92) X 10^{-5}	2.2 X 10^3
-H	170.00	6.00(6.80) X 10^{-6}	1

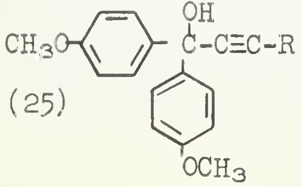
*values in parenthesis are in the presence of 0.05 M triethylamine

The following additional observations were made concerning these reactions: (1) preparative solvolyses in the presence of triethylamine or calcium carbonate gave only the corresponding acetophenones from the substituted α-bromostyrenes (24: R= $-NH_2$, $-OCH_3$ and $-NHCOCH_3$), α-bromostyrene (24: R= -H) yielded in addition 22% phenylacetylene; (2) the reaction of the p-nitro derivative was exclusively second-order and gave only p-nitrophenylacetylene; (3) each of the substituted phenylacetylenes was shown to be stable under the reaction conditions; (4) after a short warming with silver-nitrate in 80% ethanol the methoxy derivative (24: R= $-OCH_3$) gave a precipitate of silver bromide, the nitro compound (24: R= $-NO_2$) after several hours at 100° gave no precipitate; (5) and α-bromostyrene (24: R= -H) in 50% ethanol reacts ten times faster than in the less ionizing 80% ethanol solution.[32]

Based on these observations, the authors propose that the α-bromostyrene derivatives (24: R= -H, $-NH_2$, $-OCH_3$, $-NHCOCH_3$) react via an S_N1 - E1 type mechanism involving the intermediate formation of a vinyl cation, and that the nitro compound (24: R= $-NO_2$) reacts by a bimolecular elimination (E2) process. However, the following facts must be considered. First, products were never isolated from the kinetic runs themselves, and the preparative solvolyses were not run under identical conditions with the former. Secondly, no data or plots of the kinetic studies were given, only the resulting rate constants were reported. And thirdly, the authors claim that the phenylacetylene formed from α-bromostyrene (24: R= -H) could not arise from a competitive E2 process due to the small deviations observed in the first-order rate constants on addition of five molarequivalents of triethylamine. However, the question remains whether a competing E2 process could have been detected by the workers. Crude calculations indicate that a competitive E2 process here appears not unlikely. Further indication that the reactions may be more complex than the authors claim appears in the magnitudes of the relative rate constants (Table III). The reported accelerations do not parallel the known electrical properties of the substituents. In spite of these criticisms the relatively facile reaction of alcoholic silver-nitrate with the methoxy derivative (24: R= $-OCH_3$) indicates that further studies of "stacked" vinyl halide systems may prove interesting.

In a related study Grob and co-workers have examined the solvolytic decarboxylation of the potassium salts of cis and trans α,β-unsaturated-β-halo acids. Salts of the cis series when heated in aqueous solution yielded the corresponding acetylenes, while those of the trans series gave ketones in addition to acetylene derivatives. The reaction of the cis salts was explained by a concerted mechanism, on the other hand a rate-determining ionization to an intramolecularly solvated vinyl carbonium ion was proposed for the solvolysis of the trans salts.[33]

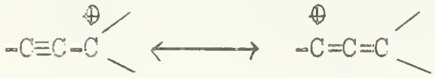
Stable cations having a contributing vinyl cation resonance form have reportedly been observed by nmr. Richey's group has examined several systems, but only the propynyl and ethynyl-di-p-methoxyphenylcarbinol (25) case will be discussed. Extraction of the propynyl compound (25: R= $-CH_3$) from carbon tetrachloride into



(25)

R= H or CH_3

concentrated sulfuric acid gave solutions whose nmr was assumed to be that of the corresponding alkynyl cation. Strong evidence for this was obtained by neutralizing the sulfuric acid solutions which gave approximately 90% of the starting alcohol. The absorption of the propynyl methyl group (τ 7.40) appeared considerably downfield from the absorption of the same group in a carbon tetrachloride solution of the substrate (τ 8.13).[34] The absorption of the corresponding ethynyl derivative (25: R= -H) showed a much larger downfield shift. (from τ 7.35 for the alcohol to τ 4.30 for the ion) The authors suggest that this indicates that the carbon to which the ethynyl hydrogen is attached is significantly involved in charge delocalization as shown by the resonance structure (26).[35]



(26)

Footnotes 36-38 are additional references to reactions in which vinyl carbonium ions have been postulated. However, due to their similarity to systems already discussed and the limited amount of information available they will not be examined in this abstract.

In conclusion, evidence presented seems to indicate that in certain systems the intermediacy of vinyl cations best explains the experimental results. Such findings cast doubt on the inferred general instability of such intermediates. In the past these intermediates have been largely rejected because of the unreactivity of vinyl halides toward alcoholic silver-nitrate. However, as several workers have pointed out,[39,40] the inertness of vinyl halides is based on ethylene derivatives and may be less applicable to more highly alkylated systems. In any case a definitive study of the reactivity of various vinyl halides toward alcoholic silver-nitrate appears to be missing from the literature. As a result the chemistry of vinyl carbonium ions is somewhat ill defined.

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SIGMATROPIC REACTIONS

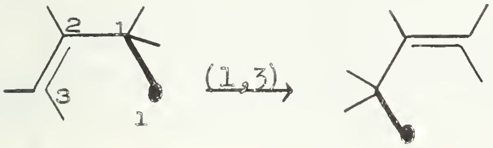
Reported by R. N. Watson May 11, 1967

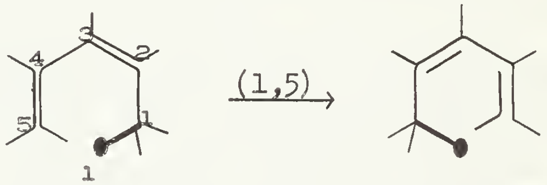
INTRODUCTION

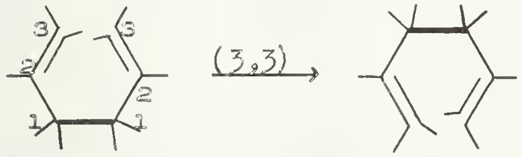
The concept of the sigmatropic reaction was derived by Woodward and Hoffmann,[1] on the basis of their molecular orbital calculations, to correlate formally a large number of separate reactions. The definition and general characteristics of sigmatropic reactions, as well as reactions which illustrate the various types of sigmatropic changes, are discussed. Emphasis has been placed on the geometry of the transition state involved in these reactions, and the correspondence with molecular orbital predictions. Although the majority of the mechanistic work has been done on thermal sigmatropic reactions, the available evidence for photochemical reactions is also considered.

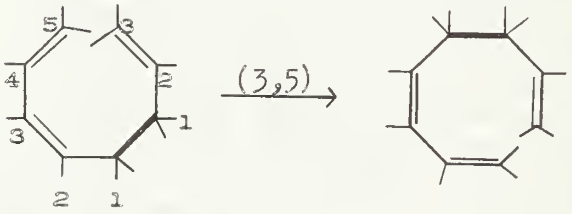
GENERAL CHARACTERISTICS

Woodward and Hoffmann[1] define a sigmatropic reaction of order (i,j) as an uncatalyzed, intramolecular reaction in which a sigma bond, flanked by one or more pi-electron systems, migrates to a new position whose termini are i-1 and j-1 atoms removed from the original bonded loci. This terminology conforms with that presently in the literature (thus a (1,5) hydrogen shift is also a (1,5) sigmatropic shift).[2] Although not specifically mentioned by Woodward and Hoffmann as criteria for sigmatropic reactions, it is found that many of the reactions are thought to be concerted, and many have been found to be reversible also. Some generalized illustrations of sigmatropic changes are given below.

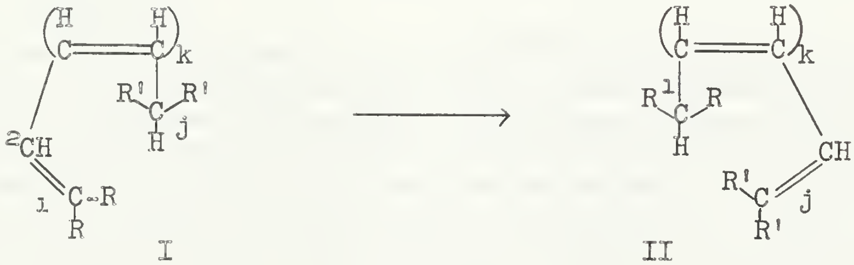








It is believed that orbital symmetry relationships are the main factors which determine the course of these reactions.[3] For example, the (1,j) sigmatropic migration of hydrogen within the all-*cis* polyolefinic framework (I → II) may take place by two paths, suprafacial or antarafacial (the transition state for this change is thought of as consisting of a hydrogen atom and a radical containing $2k + 3$ pi-electrons). In the suprafacial process, the hydrogen appears at all times



I II

on the same face of the pi-system, with the transition state having a plane of symmetry, σ. In the antarafacial process the migrating hydrogen passes from the top face of one carbon to the bottom face of another, with the transition state having a two-fold axis of symmetry, C_2.[1] It is found that, in order to maintain

positive overlap between the highest occupied orbital of the olefin system and the hydrogen orbital, the isomerization I → II must occur thermally (ground state orbital symmetry) by the suprafacial path when k is odd, and antarafacially when k is 0 or even. These results are reversed for first-excited-state transformations, and are supported by extended Huckel M.O. calculations.[3] However, if the migrating group possesses an available low-lying pi-orbital, alternative transition state processes may occur. The symmetry-allowed (1,j) sigmatropic transformations (assuming σ-orbital interaction of the migrating group with the π-system) for $j \leq 7$ are given below (Table I).

Table I[1] - Symmetry Allowed Transformations

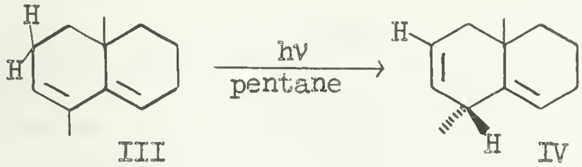
(1,j)	Thermal	Excited State
(1,3)	Antarafacial	Suprafacial
(1,5)	Suprafacial	Antarafacial
(1,7)	Antarafacial	Suprafacial

For sigmatropic reactions in which i and j are greater than 1, proceeding through transition states with a plane of symmetry, thermal changes are symmetry allowed when $i + j = 4n + 2$, whereas excited-state transformations are symmetry allowed when $i + j = 4n$.[1] Apparent sigmatropic reactions which violate these rules may be taking place through multi-step processes, perhaps involving diradical intermediates, but these are expected to require vigorous conditions.

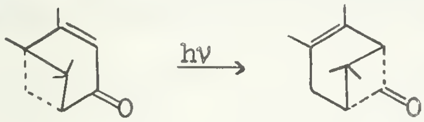
(1,3) SIGMATROPIC REACTIONS

No established examples of thermal, uncatalyzed (1,3) hydrogen shifts could be found (antarafacial). Woodward and Hoffmann believe this is because the carbon framework must not become so distorted during reaction as to cause impairment of coupling within the pi-system.[1] Thus, the antarafacial process would be difficult or impossible for $j = 3$.

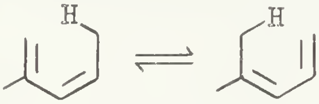
Photochemical (1,3) reactions can be postulated for at least two cases, based on product analysis. When 4,10-dimethyl-$\Delta^{3,5}$-hexalin (III) was irradiated in pentane, a 60% yield of the isomerized non-conjugated diene (IV) was isolated, along with other hydrocarbons.[4] That this reaction is intramolecular and uncatalyzed was not demonstrated, but when a similar system, 7,8:9,11-ergostadiene, is irradiated, it is found that the reaction is independent of protic and aprotic solvents and gives an isomeric non-conjugated diene with the original ergostane skeleton. No other mechanistic work was done, but a (1,3) hydrogen shift can rationalize these products. A (1,3) shift involving a carbon-carbon sigma bond was postulated[5] for the photochemical conversion of verbenone (V) to chrysanthenone (VI).



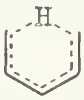
III IV



V VI



VII VIII



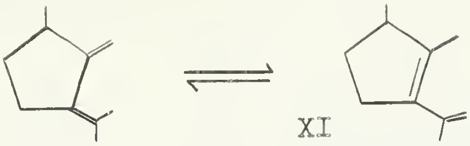
IX

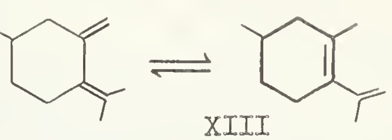
(1,5) SIGMATROPIC REACTIONS

There have been a large number of reactions[6-20,42-45] which involve the (1,5) sigmatropic migration of a hydrogen atom. Frey and Ellis[6] showed that cis-2-methyl-1,3-pentadiene (VII) undergoes a reversible, first order isomerization in the range 197-237°C to 4-methyl-1,3-pentadiene (VIII). The entropy of activation of this reaction was approximately -8 e.u., the negative value being attributed to the loss of two internal free rotations in going from the reactant to a 6-membered cyclic transition state (IX). Wolinsky and co-workers[7] observed this (1,5) migration in a number of other 1,3-dienes with a vinyl and alkyl group in a cis arrangement, while trans-1,3-dienes are stable in the same conditions. Thus the reversible rearrangement of X gives 15% XI at 260°C, and 100% XI at 360°.

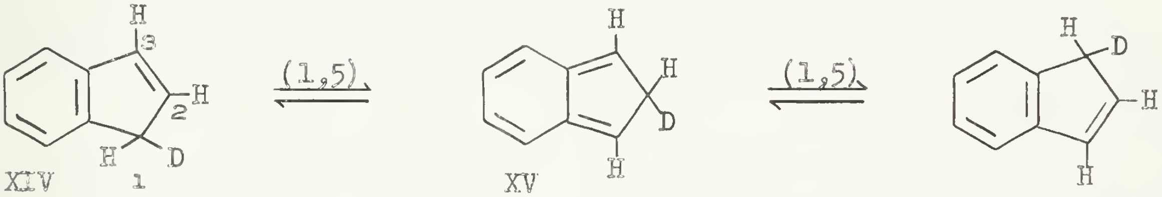
Since a higher temperature is required for the equilibration of non-planar 1,3-dienes (XII does not reach equilibrium with XIII at 450°C), and since the trans-1,3-

dienes are stable (trans-2-methyl-1,3-pentadiene gave less than 1.0% of rearrangement products at 450°), they suggest that the transition state has 5 carbon atoms in a plane (or nearly planar) with the migrating hydrogen above or below the plane. This is consistent with Woodward and Hoffmann's prediction of a suprafacial route.


X XI


XII XIII

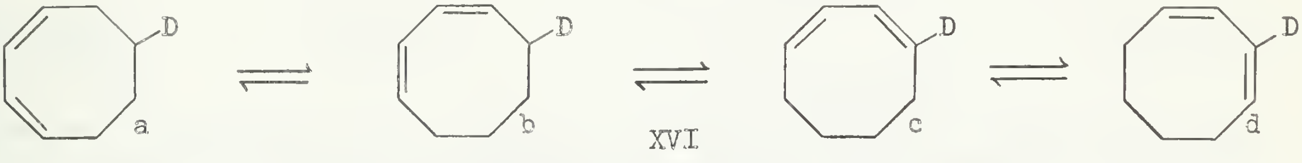
The rearrangement of cyclopentadienes also proceeds by (1,5) hydrogen shifts.[8,9] McLean and Haynes[8] determined the entropy of activation for the conversion of 5-methylcyclopentadiene to 1-methylcyclopentadiene to be -10 e.u. On the basis of an n.m.r. study of deuterated cyclopentadiene in the range 45-65°C, Roth[9] concluded that the first order rearrangement which resulted in a statistical distribution of deuterium was an intramolecular succession of (1,5) shifts. Roth also investigated the rearrangement of 1-deutero-indene (XIV) which was thought might possibly undergo a (1,3) shift (from indene to indene) in preference to a (1,5) shift (from indene to the non-aromatic isoindene (XV), then back to indene). By observing the relative intensities of the three non-aromatic hydrogen positions of 1-deutero-indene (3.18, 3.51, and 6.72τ) in the n.m.r. until the deuterium is statistically distributed, he concludes that a (1,3) hydrogen shift does not occur at all, and estimates that the energy difference between a (1,3) and a (1,5) shift in cyclopentadiene is at least 11.5 kcal./mole.



XIV XV

The thermal rearrangements of cycloheptatrienes (recently reviewed by Shermer[10]) involving the migration of hydrogen around the ring have been shown to involve the suprafacial, intramolecular (1,5) sigmatropic shift of hydrogen to the apparent exclusion of all other mechanisms.[10]

Similarly, (1,5) migrations have been observed in 8-membered ring compounds.[11-18] Careful integration of the n.m.r. spectrum at various intervals of the equilibration of neat 1,3-cyclo̎octadiene (XVIa-d) at 150° for 24 hours gave kinetic results which, according to Glass, Boikess, and Winstein,[11] are consistent only with a series of successive intramolecular (1,5) hydrogen shifts ($\Delta S^{\ddagger} = -10$ e.u.). It can be noticed that (1,5) hydrogen shifts have comparable rates and activation energies in six,[12] seven,[10] eight,[13] and nine[13] membered rings and in open-chain systems.[6,14]

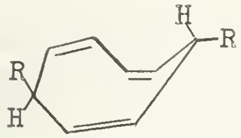


XVI

Rearrangements within the cyclo̎octatriene system are also thought to proceed by a facile (1,5) suprafacial sigmatropic shift mechanism.[13,17,18] Roth[15] demonstrated that 1,3,6-cyclo̎octatriene and 1,3,5-cyclo̎octatriene are in equilibrium at 225° by means of a (1,5) hydrogen shift. The rate of this reversible reaction is first order and is not influenced by solvent polarity. Although bicyclo[4.2.0]octa-2,4-diene is present in the equilibrium mixture, Roth believes that this is formed from the 1,3,5-triene only and is not an intermediate in the isomerization between the two. Roth rules out any large contribution due to a (1,3) shift in this isomerization by observing the rearrangement of 7,8-dideutero-1,3,5-cyclo̎octatriene. If a (1,3) shift is present the deuterium atoms would be statistically distributed through all positions on the ring, whereas for a (1,5) shift the deuteriums are limited to the 3,4 and 7,8 positions. The n.m.r. of rearranged material did not show a statistical distribution through all positions. Roth also computed the least value for the energy difference

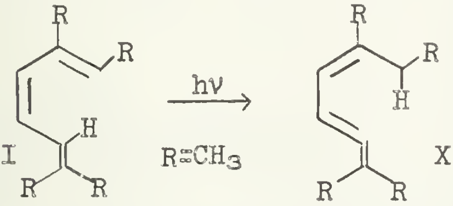
between the (1,5) shift and the hypothetical (1,3) shift to be 7.5 kcal./mole.

The rearrangement of 5,8-bis-(α-cyanoisopropyl)-1,3,6-cycloöctatriene to 3,8-bis-(α-cyanoisopropyl)-bicyclo [4.2.0]octa-2,4-diene is believed to proceed through the 1,3,5 isomer.[16] Kice and Cantrell[16] think the 1,3,6 isomer would exist preferentially with the bulky α-cyanoisopropyl groups in a quasi-equatorial configuration (XVII, R = α-cyanoisopropyl), in this configuration the migrating hydrogen would be located directly over one of the double bonds and well-situated for a suprafacial process.



XVII

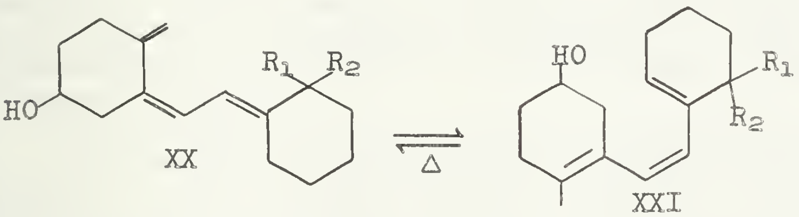
Photochemical (1,5) sigmatropic reactions (antarafacial) have been postulated to occur in several open chain systems,[18,19] but only one (8-membered) cyclic system.[20] Thus, the irradiation of allo-öcimene (XVIII) was reported by Crowley[18] to give the allene (XIX). That antarafacial (1,5) processes have not been observed for small ring compounds would seem to substantiate Woodward and Hoffmann's selection rules.



XVIII XIX

(1,7) SIGMATROPIC REACTIONS

The (1,7) sigmatropic shift should occur by the antarafacial route in ground state reactions and by the suprafacial route in excited state reactions.[1] A thermal (1,7) hydrogen migration has been proposed for the interconversion of precalciferol and calciferol and for conversions in analogous triene systems.[21-24] Schlatmann[21] converted cis-1-cyclohexylidene-2-(5'-hydroxy-2'-methylenecyclohexylidene)ethane (XX) into cis-1-(cyclohex-1'-ene)-2-(5"-hydroxy-2"-methylcyclohex-1"-ene)ethene (XXI) by heating at 70-90° for a few hours. Schlatmann determined that the reaction is found only with conjugated triene systems with a cis-configuration at the central double bond; that the reaction rate (see Table II) is independent of solvent, acids, bases, and free radical inhibitors; that there is no exchange with CH_3OD during reaction; and that the entropy of activation is negative (~ -17 e.u.).

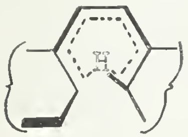


XX XXI

Table II. Rate Constants of the Isomerization ($XX \rightleftharpoons XXI$) Under Different Conditions at 60.8°C.[22]

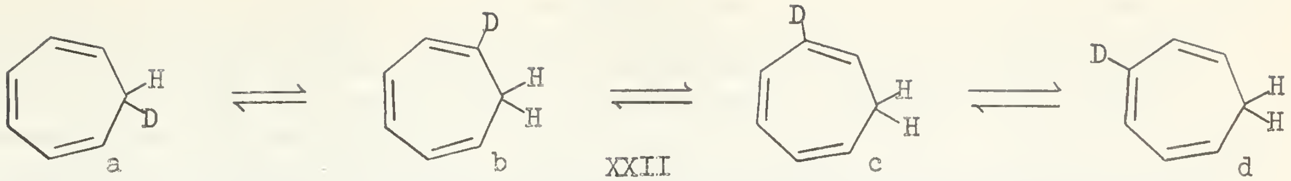
Medium	k in sec^{-1}	Medium	k in sec^{-1}
decalin	$4.1x10^{-5}$	96% ethanol + $2.3x10^{-3}M\ (C_2H_5)_3N$	$3.7x10^{-5}$
96% ethanol	$4.6x10^{-5}$		
96% ethanol + $0.8x10^{-3}MHCl$	$4.5x10^{-5}$	96% ethanol + $1.5x10^{-4}M$ hydroquinone	$4.7x10^{-5}$

Therefore he concludes that the reaction is intramolecular and occurs via a rigid cyclic transition state (XXII). The configuration of these systems will easily permit an antarafacial process.



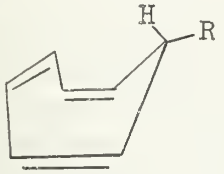
XXII

The photochemical (1,7) hydrogen shifts of cycloheptatriene systems[10,25-27] in contrast with the (1,5) thermal behavior, gives significant confirmation of Woodward and Hoffmann's selection rules. Both ter Borg[25] and Roth[26] observed a series of (1,7) shifts in 7-deutero-1,3,5-cycloheptatriene (XXIIa) by integrating the n.m.r. spectrum of irradiated samples. Both report the initial formation of the 1-deutero-isomer (XXIIb), and believe the equilibrium is completely consistent with a set of consecutive (1,7) shifts (XXIIa-d). In a similar n.m.r. study, Murray and Kaplan[27] found that, although 1,4-bis(7-cycloheptatrienyl)benzene undergoes a series of thermal (1,5) hydrogen shifts, the compound undergoes (1,7) shifts on irradiation. Their analysis of the spin-spin



XXII

coupling of this compound leads them to believe that it exists in the preferred conformation XXIII. Thus, positive overlap could easily be maintained between the migrating hydrogen orbital and a framework orbital at the terminus of the migration, thereby providing easy access to a suprafacial shift in each case.



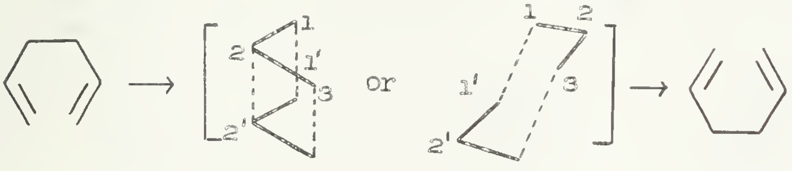
XXIII
R=4-(7-cycloheptatrienyl)-
phenyl

Although the (1,3) suprafacial shift is allowed photochemically, it has not been conclusively demonstrated as occurring in these systems concurrently with the (1,7) shift. However Murray and Kaplan[27] believe that the formation of 2-phenylcycloheptatriene instead of 1-phenylcyclopehtatriene from 7-phenylcycloheptatriene is possibly indicative of a preferential (1,3) shift over the (1,7) shift.[25] To explain the observed dominance of the (1,7) shift, Woodward and Hoffmann[1] believe that the higher values of j are preferred in order to achieve a maximum degree of linear conjugation in the transition state.

(3,3) SIGMATROPIC REACTIONS

The most well-known examples of (3,3) sigmatropic reactions are the Cope[28-32] and Claisen[33-38] rearrangements. Both reaction types are thermal (thermal changes symmetry-allowed when $i + j = 4n + 2 = 6$[1]), intramolecular, relatively insensitive to catalysis, and show negative entropies of activation, thus satisfying the general characteristics of sigmatropic reactions.[28-30] The primary concern here will be the influence of orbital symmetry in determining the orientation of the transition state in these reactions.

If the transition state of the Cope rearrangement is depicted as a complex of two allyl radicals situated in roughly parallel planes, then the question of the geometry of the transition state is whether the two allyl radicals are bound between all three pairs of atoms (six-center boat form, XXIV) or only bound through the four terminal atoms (four-center chair form, XXV).[28-30] If the rearrangement proceeds by the four-center path, then *rac*-3,4-dimethyl-1,5-hexadiene will produce only *cis*, *cis* and *trans*, *trans*-octadiene, however the *meso*-compound will produce only *cis*, *trans*-octadiene by this path.[28-31] By the six-center path, the *meso*-isomer would give a mixture of *cis*, *cis* and *trans*, *trans*-2,6-octadiene, and the racemic isomer must rearrange to *cis*, *trans*-2,6-octadiene. Doering and Roth[31] obtained almost exclusively (99.7%) *cis*, *trans*-2,6-octadiene from *meso*-3,4-dimethyl-1,5-hexadiene at 225°C, and found that the *rac*-isomer gave 10% *cis*, *cis*- and 90% *trans*, *trans*-octadiene. Therefore the rearrangement proceeds by the four-center transition state (XXV); the free energy difference between the 4-center and 6-center arrangements was calculated as at least 5.7 kcal./mole.



XXIV XXV

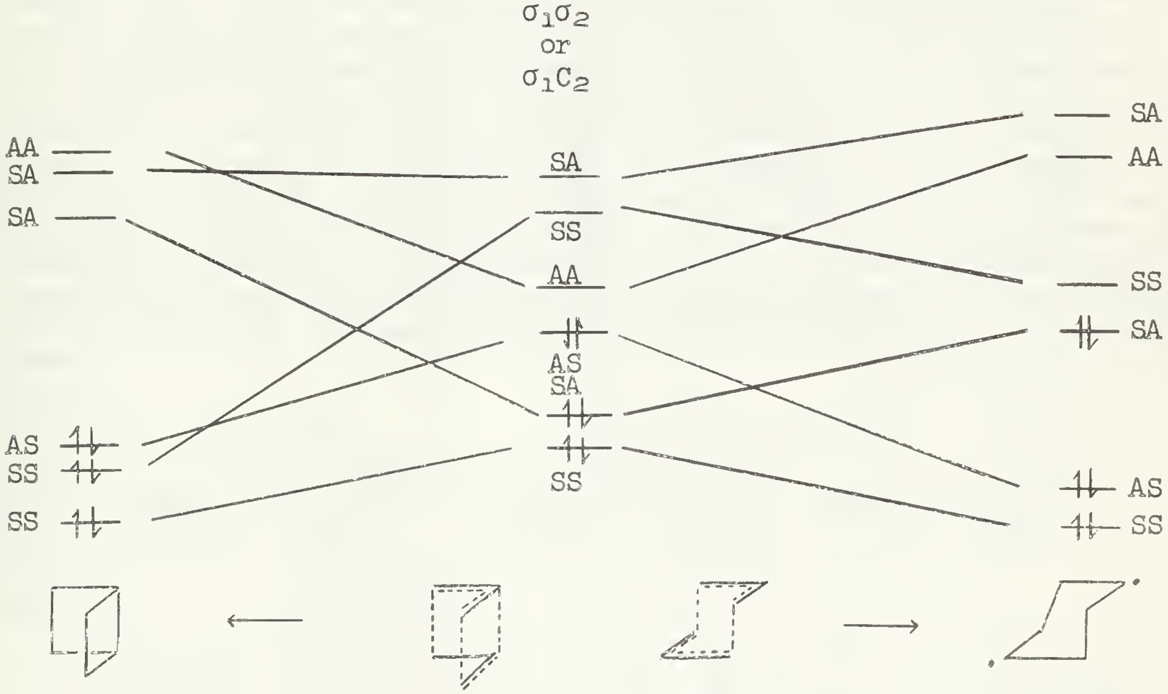
Similarly, Marvell and co-workers[36] determined by conformational analysis that the transition state of the Claisen rearrangement of *cis*- and *trans*-α,γ-dimethyl allyl phenyl ethers is best represented by a cyclic four-center chair form. From the rates of rearrangement of *cis* and *trans*-γ-substituted allyl aryl ethers and those of β-alkylallylaryl ethers, White and Norcross[33,34] also conclude that the chair configuration is preferred.

A qualitative explanation for this preference was offered by Doering and Roth.[30] In an allyl radical the energetically lowest molecular orbital contains two electrons

distributed fairly uniformly throughout the system, whereas the next higher orbital has only one electron with a very small electron density at the central carbon. Therefore two allyl radicals with this combination of orbitals will repel each other at all points and can bond only at the terminal carbons, which is best represented as the chair form.

Fukui and Fujimoto[32] applied a simple Huckel perturbation calculation to the double allyl system and determined the energy increase due to weak conjugation between atomic π orbitals at carbons 2 and 2' (of XXIV) to be $\Delta E = 2P_{22'}\gamma$, where $P_{22'} = 2\sum_{j}^{oc} C_2^j C_{2'}^j$ is a measure of the "overlap stabilization" (C_2^j and $C_{2'}^j$ denote the coefficients of $2p\pi$ atomic orbitals of the j th M.O., the summation being carried out over all occupied orbitals), and γ is the resonance energy of 2,2' conjugation. Their calculations give $\Delta E \sim 5$ or 6 kcal./mole which is consistent with Doering's[31] experimental value of 5.7 kcal./mole.

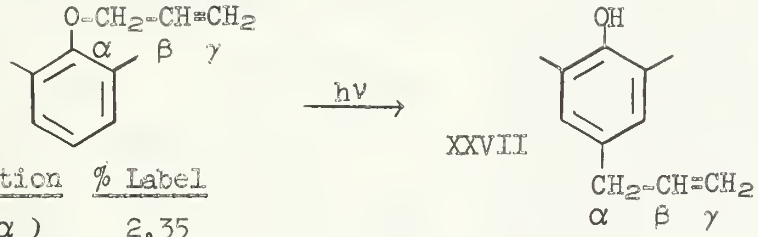
Woodward and Hoffmann,[39] in a somewhat different manner, also suggest that orbital symmetry relationships play a predominant role in determining the preference for the chair-like transition state. A correlation diagram was drawn for the hypothetical process of two allyl radicals approaching each other from infinity, in parallel planes. These motions involve two symmetry elements: σ_1, the plane passing through carbons 2 and 5; and σ_2, a plane parallel to the radical planes in the boat form, or a C_2 axis perpendicular to σ_1 in the chair form. The end products in this hypothetical motion are a bicyclohexane in the boat case and cyclohexyl biradical in the chair case.[39] The essential difference in the two approaches is in the behavior of the occupied SA level in which the boat approach correlates to an antibonding σ orbital, while in the chair form it goes over to a non-bonding radical orbital. Thus at any point, the chair-like transition state is at a lower energy as a result of the difference in the correlation properties of the SA orbital. By comparing this diagram with the actual correlation diagram for the (3,3) reaction, Woodward and Hoffmann predict that the chair form of the transition state is of lower energy.



It appears reasonably certain that the course of the (3,3) sigmatropic reactions, such as the Claisen and Cope rearrangements is determined primarily by the orbital symmetry requirements. This supports Woodward and Hoffmann's basic assumption that all sigmatropic reactions are directed by the orbital symmetry.

(3,5) SIGMATROPIC REACTIONS

The existence of the (3,5) process has not been effectively demonstrated, but it could be a partial explanation for the observation that γ-^{14}C-allyl-(2,6-dimethyl phenyl)-ether (XXVI) rearranged under irradiation for 2 1/2 days at 25° to give 1.4% of the 4-allyl phenol (XXVII) with label distributed fairly evenly in the α and γ positions (at 20-30° the rate of the thermal rearrangement is practically zero, and would give 100% retention of label in the γ position).[40] Since 2,6-dimethyl phenol was formed in 9% yield in these same conditions, this could be a case of dissociation to free radicals and recombination. A more definitive examination of this reaction was not done.



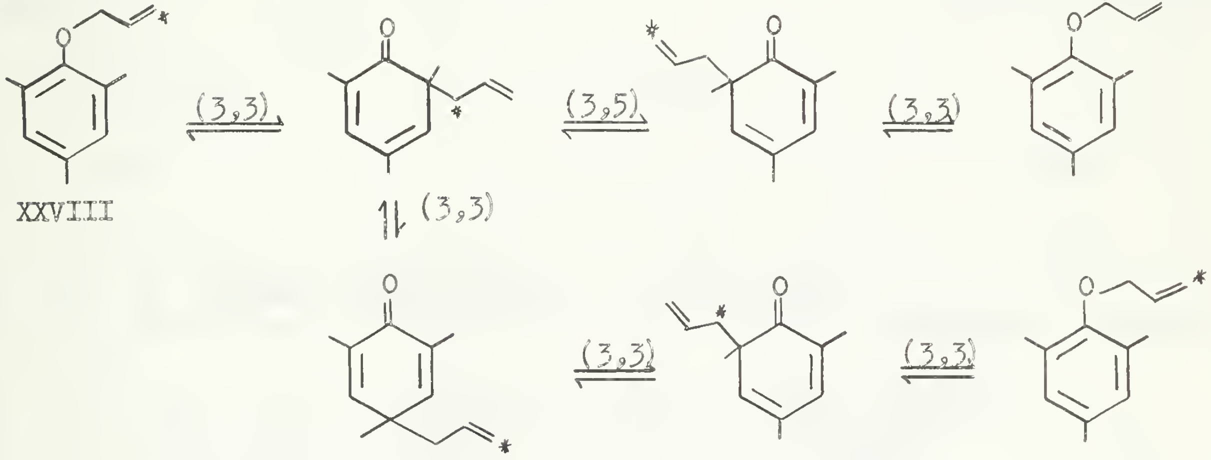
XXVI

Position	% Label
α β	2.35
γ	97.4

XXVII

Position	% Label
α β	47
γ	53

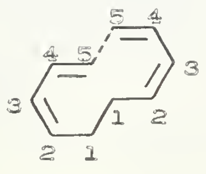
A thermal (3,5) type process has been considered by Fahrni and Schmid[29,41] to explain the isotopic distribution obtained by heating allyl-γ-^{14}C-mesityl ether (XXVIII-is not capable of phenol formation) for 96 hours at 170° in diethylaniline. The heated material had radioactivity almost evenly distributed between the α and γ atoms, whereas the starting material had label exclusively in the γ atom of the allyl group. This result is not possible by the accepted Claisen mechanism of a sequence of (3,3) steps.[29] A possible pathway which could account for this result and still preserve the observed intramolecular character of the rearrangement is a (3,5) sigmatropic ortho-ortho' rearrangement. This type of rearrangement may also explain small discrepancies in the isotopic distribution found in the equilibrium of other allyl ethers.[29] Although reasonable, this mechanism has yet to be fully established.



XXVIII

(5,5) SIGMATROPIC REACTIONS

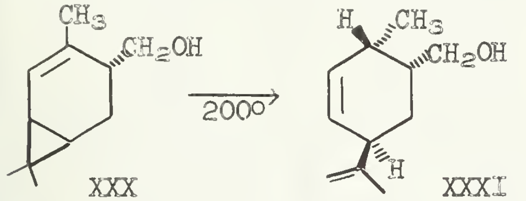
Woodward and Hoffmann[1] as well as Fukui and Fujimoto[32] predict from molecular orbital considerations that a chair-like transition state would be preferred in the (5,5) sigmatropic shift of cis, cis-decatetraene (XXIX).



XXIX

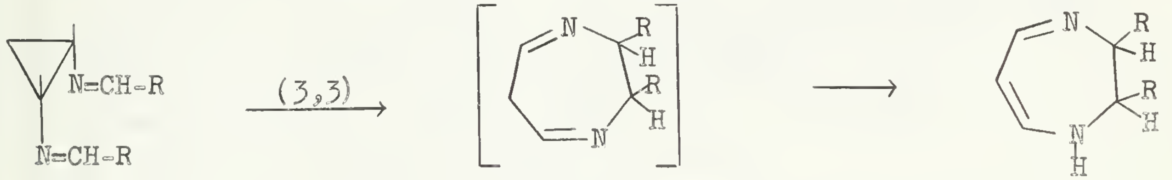
SIGMATROPIC REACTIONS INVOLVING CYCLOPROPANE RINGS AND HETEROATOMS

It has been noted that a cyclopropane ring may replace a π-bond in the framework system for sigmatropic changes.[1] This observation has been very well documented in the literature.[11,13,14,30,42-45] It has been found that cis-1-methyl-2-vinylcyclopropane rearranges by a (1,5) shift at temperatures above 160° to cis-hexa-1,4-diene,[42] (+)-trans-3-hydroxymethyl-Δ^4-carene (XXX) rearranges stereospecifically (suprafacial) at 200° to (-)-6-hydroxymethyl-$\Delta^{2,8}$-p-menthadiene (XXXI),[14] 1,4-cyclooctadiene and bicyclo[5.1.0.] oct-2-ene are in thermal equilibrium above 180° ((1,5) shift),[43] and (1,5) sigmatropic shifts are observed in the rearrangements of bicyclononadienes to cyclononatrienes.[11,13,45] Cyclopropyl ring intermediates are proposed for the Abnormal Claisen rearrangement[46,47] and similar systems.[48-50]



XXX XXXI

The incorporation of an oxygen in the framework system has already been noted in the Claisen rearrangement. There is evidence that nitrogen may also participate in sigmatropic reactions. Staab and co-workers[51-54] believe a Cope type (3,3) sigmatropic rearrangement (XXXII → XXXIII) occurs in the thermal isomerization of double Schiff bases of 1,2-diaminocyclopropane (XXXII) to 2,3-disubstituted-1H,1,4-diazepines (XXXIV). An extreme example of the variations possible in the (1,5) sigmatropic reaction is given by the rearrangement of 1-(p-nitrobenzoyl)-2,2-dimethyl aziridine (XXXV) to N-(β-methallyl)-1-p-nitrobenzamide (XXXVI) in which a 3-membered ring, nitrogen, and oxygen atoms participate in the framework system.[55-56]



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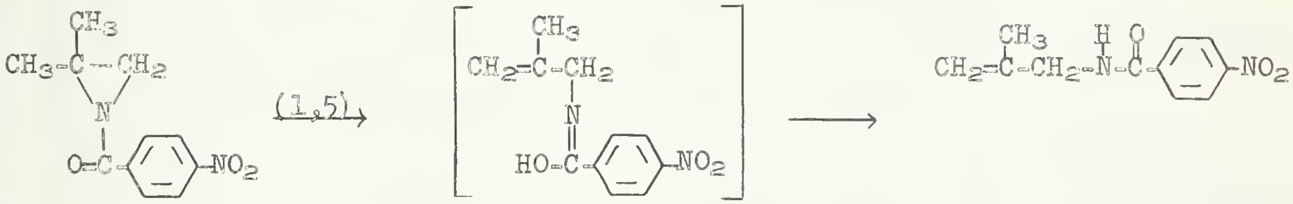

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PHOTOCHEMISTRY OF CYCLOBUTANONES AND CYCLOBUTANEDIONES

Reported by Edward F. Johnson May 15, 1967

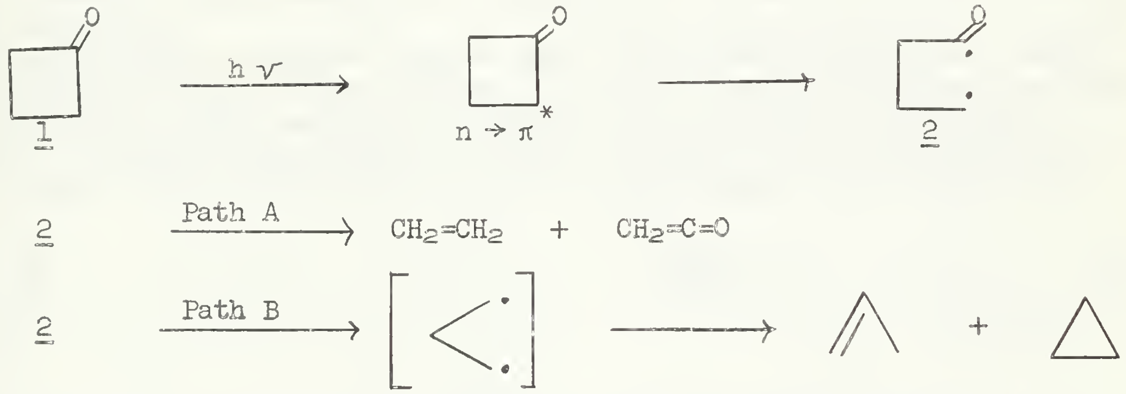
CYCLOBUTANONES

The photochemistry of cyclobutanone in the gas phase has been reviewed by Srinivasan[1] and compared to the known photochemistry of other cyclic ketones. In general, the primary photochemical process for cyclic ketones is thought to be a ring opening to a biradical which then undergoes rapid dissociation to stable molecules. Carbon monoxide is split out, leaving cyclic hydrocarbons and various olefins; in addition, unsaturated aldehydes are formed by abstraction of a β hydrogen. Cyclobutanone undergoes vapor phase reactions similar to those of its higher homologs, with the exception that only a very minor amount of the unsaturated aldehyde is formed.[2]

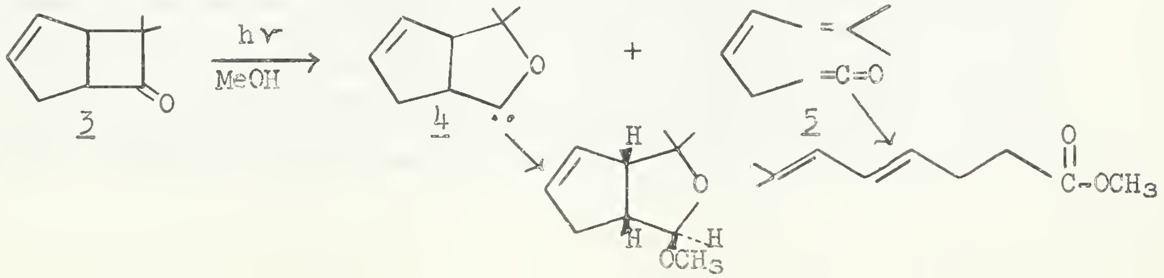
Photolysis of cyclic ketones in the liquid phase is often dependent on the choice of solvent.[3] The first step in the photochemical process can be formally represented by the fission of a CO-C bond to give, most commonly, the most substituted aryl/alkyl biradical. The biradical will then stabilize itself by one of three paths; (a) hydrogen transfer from the carbon atom α to the carbonyl group to form a ketene, (b) hydrogen transfer to the carbonyl group to form an unsaturated aldehyde, or (c) loss of carbon monoxide. The loss of CO, well known in the gas phase, is seen only for certain ketones in the liquid phase.[4]

The photolysis of cyclobutanone in inert solvents has been found to give the same products as in the gas phase; namely ethylene, ketene, propylene, and cyclopropane.[5,6] This decomposition, both in vapor and condensed phases, can be explained in terms of one primary photochemical process (scheme 1) in analogy to the bond cleavage reported for the vapor phase reactions of other cyclic ketones. First, there is an α cleavage from the n → π* state of 1 to yield the hypothetical biradical 2 which decomposes by either cycloelimination or decarbonylation, pathway A or B, respectively.

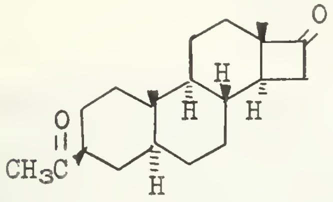
Scheme 1



In the presence of a reactive solvent, a third decomposition pathway is seen to be operative. Hostellter[7] irradiated the bicyclic ketone 3 in methanol and isolated two products in nearly equal amounts. He proposed the carbene 4 and the ketene 5 as intermediates to explain the products. No direct evidence was presented for the presence of the carbene.



Quinkert, Cimbollek, and Buhr[5] have examined the photochemistry of C-13 epimeric D-nor-16-keto steroids 6 and 7.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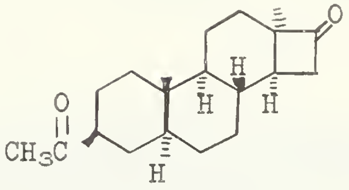
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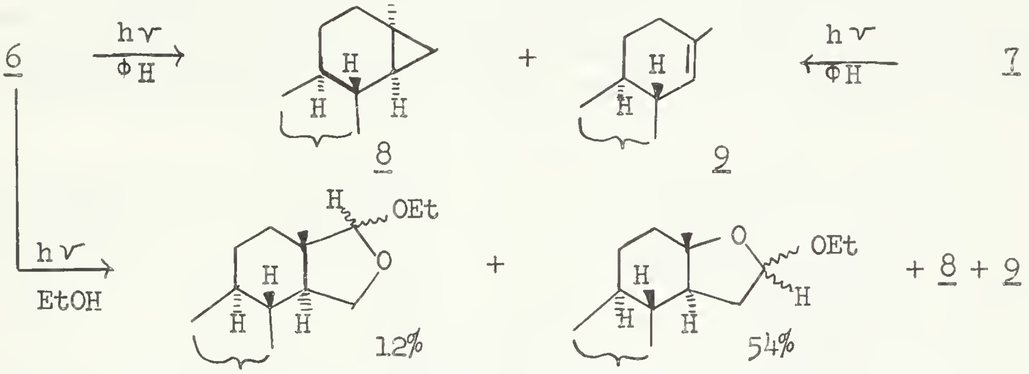
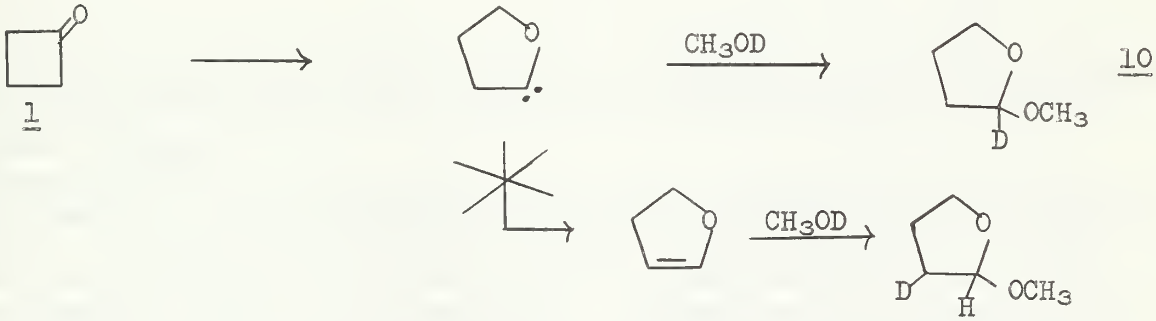
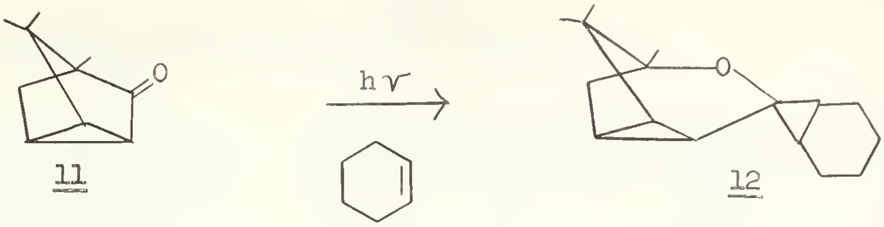
In benzene, 6 and 7 give the decarbonylation product 8 and the cycloelimination product 9 in product ratios of 61:39 for 6 and 8:92 for 7. On the other hand, acetals are the major products if the steroid is irradiated in ethanol solution as shown in scheme 2. Steroid 7 also gives products showing complete retention of configuration. The configuration was determined by spectral properties and by chromic acid oxidation to the lactone. The resulting lactones were compared to authentic samples prepared from the original steroids by Baeyer-Villigar oxidation. Therefore, the retention of configuration seems to rule out a "free" alkyl/acyl biradical.

Scheme 2



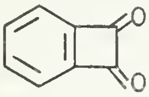
Turro and Southam[6] have also studied this ring expansion reaction. Irradiation of cyclobutanone in deutero-methanol leads to nearly exclusive formation of 10. This product offers additional support for the carbene intermediate, and rules out a potential mechanism involving a hydrogen shift and addition of methanol across a double bond. The cleavage has been shown to favor the most substituted bond α to the carbonyl group. If 2,2-dimethylcyclobutanone is irradiated, none of the acetal resulting from the cleavage of the C_4—O bond is found. Cyclopentanone, when irradiated in ethanol, does not undergo ring expansion, but forms 4-pentenal instead. Yates and Kilmurry[8] report a case in which a tricyclic cyclopentanone undergoes ring expansion by way of an oxocarbene. If d-cyclocamphanone, 11, is irradiated in cyclohexene, the carbene is trapped, and the resulting product was isolated and shown to be 12.





BENZOCYCLOBUTENEDIONES

Oxocarbenes have also been proposed in the photolysis of benzocyclobutenedione, 13, in solution. Brown and Solly[9] have isolated two dimers in the photolysis of 13 in degassed cyclohexane using natural sunlight filtered through pyrex. The dimers, 14 and 15 (5.5 and 38% yield respectively), are proposed to result from the reaction of the oxocarbene 16 with 13 or an excited state of 13. More definite evidence for the oxocarbene results from the work of Staab and Ipaktschi.[10] They irradiated 13 in pentane; methylene chloride (2:1) solutions at 20° using a mercury high pressure lamp and isolated three dimers; 14 (25%), the *cis* isomer of 14 (5%), and 17 (4%). No evidence is presented to show whether 17 is formed as a result of a photochemical process on 13 or as a result of rearrangement of another product. The oxocarbene 16 is trapped as the ethyl acetal by irradiating 13 in refluxing alcohol; while a control experiment carried on without irradiation yielded no acetal after refluxing in alcohol for 12 hours.



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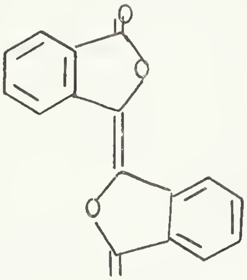

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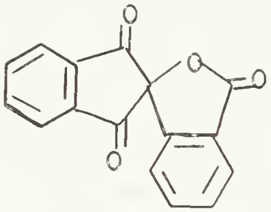

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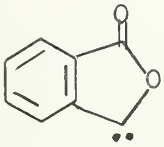

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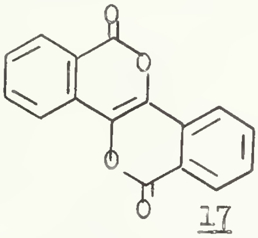

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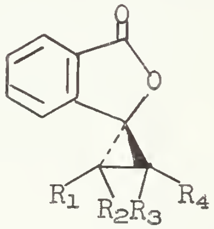

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Irradiation of 13 in excess alkenes (propylene, isobutylene, cyclohexene, butadiene, and ethyl vinyl ether) at 20° for 24 hours gave the spiro-lactone structure 18.

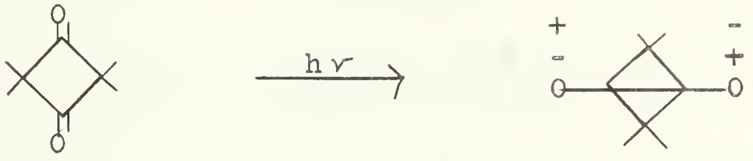
CYCLOBUTANE-1,3-DIONES

An examination of the ultraviolet spectrum of tetramethylcyclobutane-1,3-dione, 20, showed an $n \to \pi^*$ transition in the 300 mμ region.[12] Kosower[13] observed a second $n \to \pi^*$ transition in the 340 mμ region. The low intensities of the transitions as well as both the direction and the magnitude of the solvent effects are consistent with $n \to \pi^*$ transitions. The bands are observed at 348 mμ (ϵ 18) and 308 mμ (ϵ 39) in iso-octane; 344 mμ (ϵ 18) and 304 mμ (ϵ 30) in ethanol. The two different transitions are explained by an interaction between the carbonyl groups in the excited state and are described as follows:

A $n \to \pi_1^* + \pi_2^*$ (340 mμ band)

B $n \to \pi_1^* - \pi_2^*$ (300 mμ band)

The excited state A may be pictured as shown below.

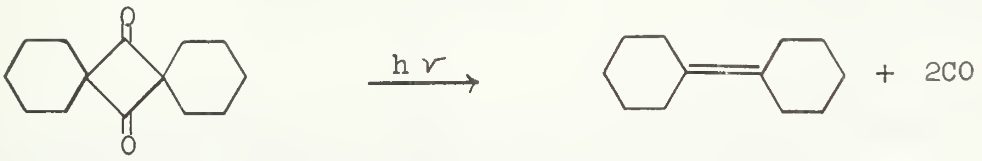


20 A

The photolysis of tetramethylcyclobutane-1,3-dione in the vapor phase had been carried out by Turro, Leermakers, Wilson, Necker, Byers, and Vesley.[14] They found that complete photolysis at low pressure yields 2.0 moles of carbon monoxide, 0.078 moles of propylene, 0.0024 moles of methane, and a trace of propane for every mole of the dione. There is a slight induction period in the evolution of carbon monoxide and a rather obvious induction period for propylene. This difference, and also the low yield of olefins compared to the production of carbon monoxide, is explained by the early formation of high molecular weight polymers which were observed on the sides of the reaction vessel. The photolysis was carried out using pyrex vessels and mercury arc lamps. These conditions were used for all the experiments reported in the remainder of the seminar, unless otherwise noted.

Several groups of workers have looked at the photolysis of the dione in inert solvents. Cookson, Nye, and Subrahmanyam[15] have irradiated 20 in benzene solution. They obtained tetramethylethylene (80% yield) and carbon monoxide. Turro and co-workers[16] observed that a ketene is also a product of the reaction. Evidence for the presence of dimethylketene is suggested by the yellow color of the reaction mixture, the strong infrared band at 2124 cm^{-1}, and the disappearance of both the yellow color and the 2124 cm^{-1} band when iso-propyl alcohol was added. The quantum yield for the disappearance of 20 was 0.38 ± 0.01.

The formation of an olefin and carbon monoxide seems to be a general reaction for tetra-substituted cyclobutane-1,3-diones. The exhaustive photolysis of dispiro[5.1.5.1]-tetradecane-7,14-dione, 21, in degassed benzene and methylene chloride yields bicyclohexlidene (70% yield) and CO.[14] If a benzene solution



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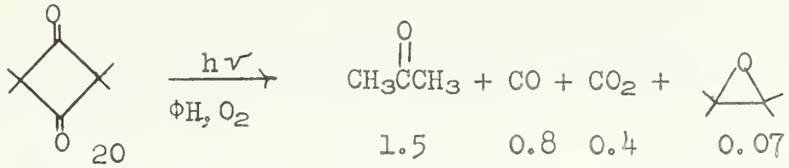
of tetramethyl- and tetraethylcyclobutane-1,3-dione is photolyzed, high yields of the expected tetramethyl- and tetraethyl- olefins are obtained, but no dimethyldiethylethylene could be detected (limit of detection about 0.1%). The yellow color of a ketene was also observed in the latter reaction.

If the photolyzed solution of 20, after low conversion, is analyzed by vapor phase chromatography (vpc), the presence of a new component is detected in significant amounts. This new component corresponds to isopropenyl isopropyl ketone, 22, and after isolation by vpc, was shown to be identical to an authentic sample. However, an examination of the reaction mixture by spectral methods showed the ketone 22 to be absent. Therefore, it was thought that the ketone 22 was formed as a result of decomposition of an unknown precursor upon analysis by vpc. As the photolysis of 20 proceeded, 22 reached a steady state but dropped to 1/4 if the reaction mixture was allowed to stand in the dark for 15 hours.

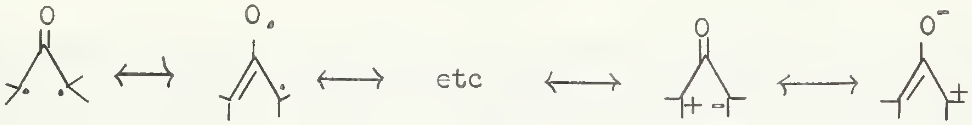
If dione 20 is photolyzed in benzene under 540 mm of oxygen and the reaction is followed by mass spectroscopic and vpc studies, the products shown in scheme 3 are observed (with appropriate mole ratios).[17] No isopropenyl isopropyl ketone[22] was detected by vpc. It was shown that both the ketone 22 and tetramethylethylene were stable to both light and oxygen under the reaction conditions. Therefore,

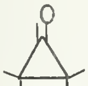
Scheme 3



the precursor of ketone 22 forms tetramethylethylene under degassed conditions and acetone and tetramethylethylene oxide in the presence of oxygen.

Much evidence has been presented that the precursor of isopropenyl isopropyl ketone is tetramethylcyclopropanone, 23, or its excited state, for which many resonance forms can be drawn as shown below. Several workers have been successful in trapping the cyclopropanone intermediate and finally in isolating it from the reaction mixture. Richey, Richey, and Clagett[18] irradiated tetramethylcyclobutane-1,3-dione in 5% solutions of ethanol and were able to isolate tetramethylcyclopropanone ethyl hemiketal, 24, in 35% yield by recrystallization and 55% yield by vpc. Also detected were the esters 25 (20-25%), 26, and 27 and ketone 28. The last three were found in 10-15% yield and were believed to result from decomposition of the hemiketal. Isolation and the resulting decomposition of the pure hemiketal have shown this assumption to be correct.[19]





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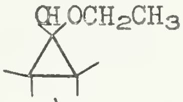

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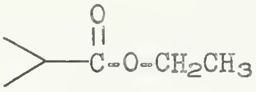

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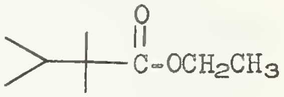

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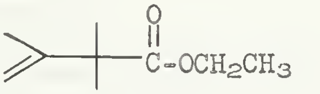

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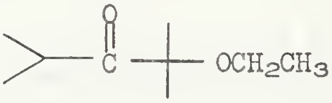

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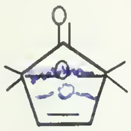

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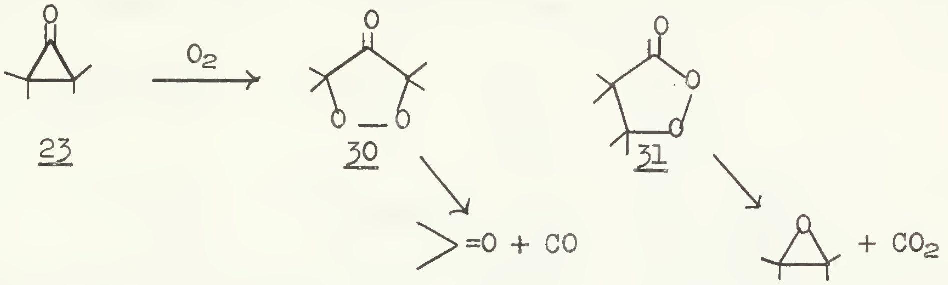
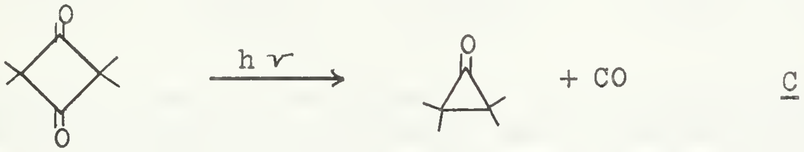
Turro and co-workers[14,16] obtained corresponding products from the photolysis of the dione in methanol. They also detected a 5% yield of tetramethylethylene. The quantum yield for the disappearance of 20 in methanol was found to be 0.49 ± 0.03. Cookson and co-workers[15] carried out the photolysis in the presence of furan and isolated adduct 29 in 15% yield after distillation. Turro and co-workers[20] were able to isolate tetramethylcyclopropanone, 23, and examine its properties. Saturated pentane solutions of the dione 20 were photolyzed in a pyrex Hanovia 450-w immersion apparatus at 36° for 1 to 2 hours. Longer reaction times cut down the yields of the cyclopropanone. The resulting solution was stripped of the tetramethylethylene and pentane until an approximately 10% solution of 23 was obtained (estimated by infrared spectroscopy). This remaining pentane solution of 23 was purified by bulb to bulb distillation at 1 mm and 20°. A band for the C=O stretching frequency was found at 1840 cm^{-1}, which would be expected for such a small ring carbonyl compound. They found that the infrared band disappears when either furan, oxygen, or methanol is added to the pentane solution. When injected into the vpc, 23 rearranges to isopropenyl isopropyl ketone. The authors concluded that tetramethylcyclopropanone "is a fairly stable, distillable compound which can be handled in pentane solution." Furthermore, all the various trapping experiments to prove the

intermediacy of 23 in the photolysis of the dione 20, are valid. In fact, all the reactions reported for tetramethylcyclopropanone under the photolysis conditions will also proceed in the absence of light starting with pentane solutions of the cyclopropanone. The oxidation of 23 in the presence of oxygen is thought to proceed through the peroxides 30 and 31 which decompose to the observed products, acetone and tetramethylethylene oxide.[14,17]

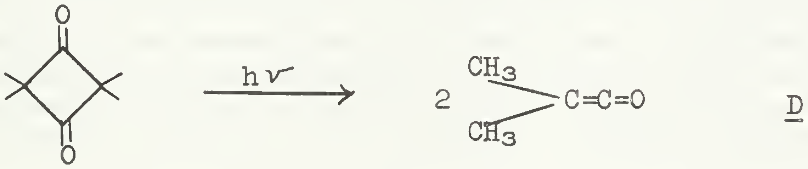


By using pyrex glass the excitation was primarily located in the lowest energy transition of the dione (the 340 mμ region). The use of filters to excite only the lowest energy transition did not appear to alter the course of the reaction.[14] No fluorescence or phosphorescence from 20 was detected at 77°K in an ethanol:ether:isopentane matrix. The lack of emission from 20 implies an extremely rapid path of deactivation from the lowest excited state. There is some indirect evidence which indicates that the chemically active state is the $n \rightarrow \pi^*$ singlet. Since the quantum yield for decomposition of 20 is high, the most likely paths for deactivation of the lowest excited state are (a) photochemical reaction, or (b) intersystem crossing to the lowest triplet, followed by decomposition. The photolysis of the dione is neither sensitized by benzophenone (E_T = 69 kcal per mole) nor quenched by 1,3-pentadiene (0.3M). These facts imply that the lowest triplet is not involved. However, this result is not conclusive because the triplet of benzophenone may not be of sufficient energy to excite the dione, and the decomposition of dione in the triplet state may be faster than energy transfer to the quencher.

In order to decide what the primary photochemical processes in the photolysis of tetramethylcyclobutane-1,3-dione were, Haller and Srinivasan[21] took the infrared spectrum of the reaction mixture as soon as possible after photolysis by using a cell which allowed direct infrared analysis at variable temperatures. The reaction was studied at room temperature and in a nitrogen matrix at 4°K, and conversion of 20 to products was held to 10% or less to insure that no secondary processes would take place. The workers were able to follow the production of tetramethylcyclopropanone by a band at 1840 cm^{-1} and the dimethylketene by a band at 2124 cm^{-1}. Both bands were observed at both temperatures indicating two primary photochemical processes were taking place, as shown in processes C and D.



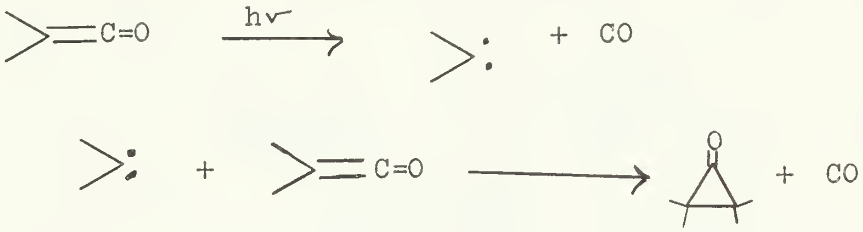
C



D

From the extinction coefficient of dimethylketene (at 2124 cm^{-1}), it is estimated that this product accounts for at least 20% of the disappearance of the dione. Concurring results also were obtained by an ultraviolet study. The yield of esters formed when alcohol reacts with the dimethylketene has already

been shown to be between 20-30%,[14,18] which agrees with the physical data. However, process D severely complicates the photochemistry of 20 for the following reasons: 1) If dimethylketene is irradiated at 2537 Å in cyclohexane using a vessel with KBr windows, tetramethylethylene, carbon monoxide, and tetramethylcyclopropanone are observed. Since conversion was kept negligibly small, the cyclopropanone must come only from dimethylketene. The reaction can be explained in the following manner. The photolysis of dimethylketene in the vapor phase

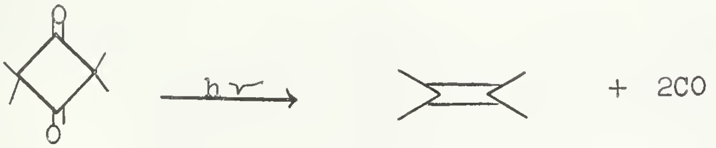


yields dimethyl carbene at either 2537 or 3660 Å, although the quantum yield is much lower when the higher wavelength radiation is used.[22] An analogy for the latter reaction is the known procedure for making cyclopropanones from diazomethane and ketenes.[23] Therefore, photolytic decomposition of dimethylketene may also be a source of tetramethylethylene and tetramethylcyclopropanone when the dione is photolyzed in an inert solvent. 2) If oxygen is bubbled through a solution of dimethylketene in cyclohexane, the band at 2124 cm^{-1} disappears and new bands are seen at 2324 cm^{-1} (CO_2) and 1720 cm^{-1} (acetone). 3) Dimethylketene is known to undergo dimerization exclusively to tetramethylcyclobutane-1,3-dione at room temperature.[20,24]

If oxygen is added to a partially photolyzed solution of the dione, the ketene disappears quickly, but the cyclopropanone is found to diminish rather slowly.[21] This reaction casts doubt on the efficiency of oxygen as a trapping agent for the cyclopropanone. However, Turro and co-workers[20] claim that when oxygen is added to a pentane solution of isolated tetramethylcyclopropanone, it disappears very quickly. No apparent reason is offered for this conflict.

By assuming that the extinction coefficient for cyclopropanone is the same as for cyclobutanone, Haller and Srinivasan[21] estimate that the primary process C is of no more importance than process D. Therefore since there are 2 moles of dimethylketene for every mole of tetramethylcyclopropanone, primary process D accounts for no more than 40% of the disappearance of the dione.

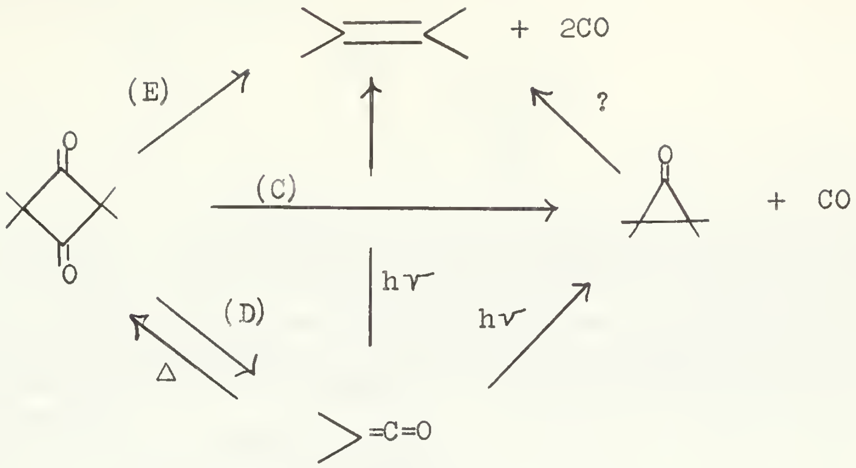
These same workers found still a third primary process which is important.[25] This process involves the loss of 2 moles of CO to form tetramethylethylene directly. Evidence for this process was a band at 1176 cm^{-1} in the infrared spectrum



E

of the photolyzed dione, at low conversion, in a nitrogen matrix. This band was assigned to the ethylene derivative. Better evidence for process E was provided by an ultraviolet study of a cyclohexane solution of the dione 20. The spectrum showed a marked increase in absorption in the region of 240 to 200 mμ on photolysis, at low conversion, in a quartz cell. The contribution to this band by dimethylketene was determined to be minor, while the contribution due to the cyclopropanone derivative was even less. In control experiments it was shown that this absorption was not due to products from the reaction of ketene with water or oxygen.

A summary of the reactions taking place when tetramethylcyclobutane-1,3-dione is photolyzed is shown in the following scheme:



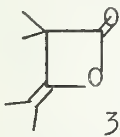
20

It is difficult to estimate the extent of processes C and E for several reasons. First, the secondary processes give products identical to those formed in the primary processes. Second, the nature of the process which converts tetramethylcyclopropanone to tetramethylethylene is unknown. However, direct photolysis of the cyclopropanone is unlikely at low conversion of 20, so that the presence of tetramethylethylene in the early stages of the reaction, requires the third primary process. As reported earlier in the seminar, trapping experiments showed 5% substituted ethylene present when the cyclopropanone was trapped by an alcohol and in the presence of a high pressure of oxygen. However, as it has been pointed out, oxygen may or may not be a good trapping agent.

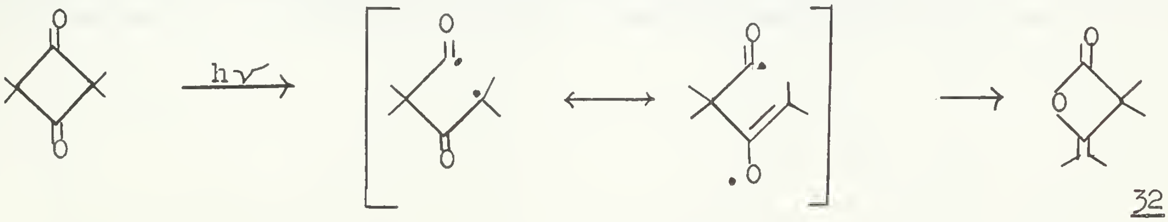
It has been shown earlier that there is an interaction between the carbonyl carbon atoms in the excited state of the dione.[13] This effect could decrease the distance between the other two carbon atoms which would be required for the simultaneous loss of two carbon monoxide molecules.

Process E, according to Srinivasan,[25] accounts for 40% of the disappearance of the dione. However, Turro[14] maintains that the trapping of cyclopropanone with oxygen, furan or an alcohol is complete, and this trapping process accounts for a majority of the disappearance of the dione. Process E accounts for only 5%. Srinivasan[21] points out the trapping experiments may not be valid for the following reasons:
a) Oxygen, furan, or an alcohol may react with an excited state precursor of tetramethylcyclopropanone, which otherwise may lead to other products such as the substituted ethylene. b) A solvent effect may change the course of the reaction in a more polar solvent.

Prolonged photolysis of tetramethylcyclobutane-1,3-dione leads to still another product, the lactone 32, in low yields.[20] Product 32 might be thought of as a dimerization product of dimethylketene. However, the thermal dimerization of dimethylketene leads exclusively to the tetramethylcyclobutane-1,3-dione.[24] A photochemical reaction of dimethylketene under the same conditions of the photolysis reaction of the dione, did not lead to significant amounts of the lactone.[20] A possible mechanism for the lactone reaction is shown below. Cookson and co-workers[26] have also reported a low yield of the lactone, along with other products, in the photolysis of 20.



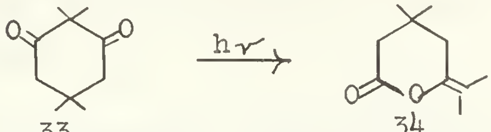
32



32

They have also shown that this lactone formation takes place in other cyclic

diones. For example, when 2,2,4,4-tetramethyl-cyclohexane-1,3-dione is irradiated, lactone 34 is found in 35-56% yield.



33 34

CONCLUSION

Cyclobutanone has been found to undergo most reactions expected for a cyclic ketone; however, in alcohol solvents, a ring expanded acetal product has been observed. This product is believed to result from a carbene intermediate. An oxocarbene intermediate is also proposed in the photolysis of benzocyclobutenediones to yield ring expanded acetals. The photolysis of cyclobutane-1,3-diones has been found to go by three different paths. The secondary processes combine to make the understanding of the various primary processes difficult.

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THE MECHANISM OF PAPAIN CATALYSIS

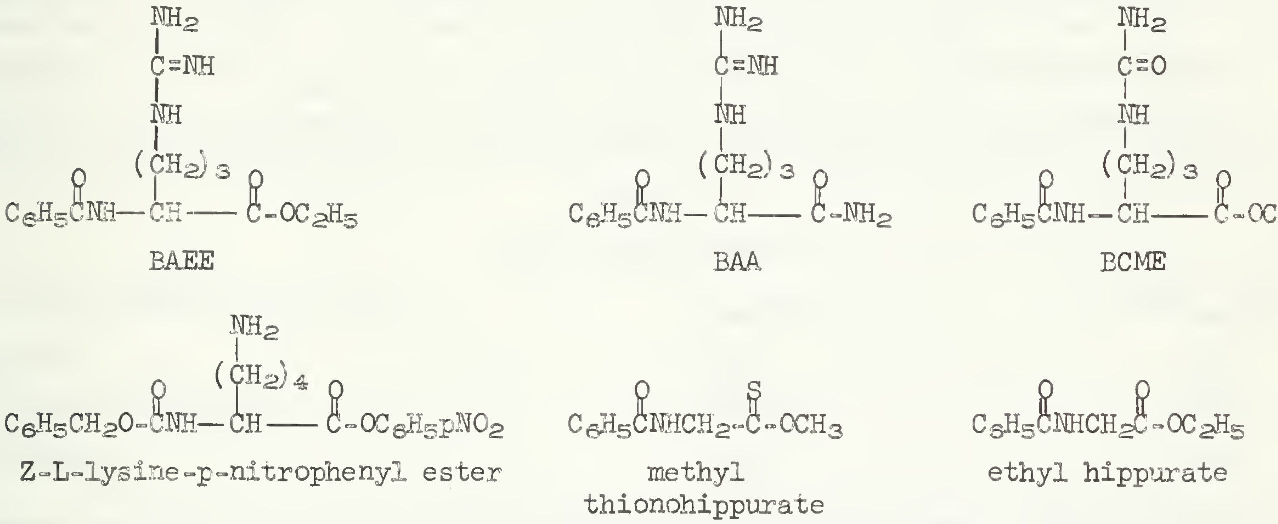
Reported by Paul Elliot Bender May 18, 1967

INTRODUCTION*

Papain is a crystalline proteolytic enzyme found in highest concentrations in the secreted fluid of latex vessels under the skin of the tree Caprica papaya.[1] Named in 1879 by Wurtz and Bouchut,[2] who performed the first well controlled experiments on the crude extract, it has played an important role in the establishment of many basic facets in our present conceptions of enzyme action.[1] The literature concerning papain has been extensively reviewed to 1962.[1,3,4-6] A review of the work on primary structure appeared in 1964[7] and some findings of more recent studies, (1965), have been outlined.[8] This seminar will emphasize the material of the last four years concerning the mechanism of the papain catalyzed hydrolysis of synthetic substrates.

ACYL ENZYME INTERMEDIATE

The first direct evidence of an acyl papain derivative was the observation by Lowe and Williams,[9,10] in a difference spectrum, obtained thirty seconds after adding methyl thionohippurate shown in Figure I to the activated buffered enzyme, of a single U.V. absorption band at λ_{max} 313 mμ ($\log e_{max}$=4.3 ± 0.3) whose O.D. dropped to 0 in 12.5 minutes. From a comparison to the model compounds shown in Table I[10] below, the authors suggested that the group most comparable in terms of λ_{max} and


BAEE

BAA

BCME

Z-L-lysine-p-nitrophenyl ester

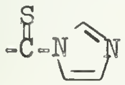
methyl thionohippurate

ethyl hippurate

Figure I. Structural Formulas

Table I

Acyl Enzyme Models

Chromophore	$\lambda_{max}^{(1)}$ (mμ)	$\log e_{max}$	$\lambda_{max}^{(2)}$ (mμ)	$\log e_{max}$
ethyl dithioacetate	305	4.08	460	1.25
methyl thionohippurate	230	4.26		
	291	4.00	250	4.00

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*In this paper α-N-benzoyl-L-arginine ethyl ester, α-N-benzoyl-L-argininamide, α-N-benzoyl-L-citrulline methyl ester, and α-N-benzyloxycarbonyl will be abbreviated as BAEE, BAA, BCME and Z, respectively.

Table I (Cont.)

Chromophore	$\lambda_{max}^{(1)}$ (mμ)	log e_{max}	$\lambda_{max}^{(2)}$ (mμ)	log e_{max}
$-\overset{S}{\overset{\|}{C}}-NH_2$	358	1.25	268	4.05
papain at pH 7	278	4.71		

log e_{max} whose presence in the intermediate could account for the observed difference spectrum, is the dithioacylester moiety. It is quite obvious that both the substrate and the enzyme absorb well below 313 mμ. Upon adjustment of the pH from the initial 6.0 to 2.5 (where denaturation is known to occur)[11] the 313 mμ band shifted to 309 mμ and the absorption was maintained.

The spectral evidence for the second acyl enzyme, trans-cinnamoyl papain,[12,13] also had to be obtained via a difference spectrum, since for this acyl intermediate, the rate of deacylation is comparable to that of acylation. To prepare a partially acylated enzyme, excess trans-cinnamoyl imidazole was added to a pH 3.43 buffered activated papain solution. After five minutes the mixture was chromatographed on a Sephadex G-25 column to isolate the acyl enzyme. The difference spectrum of a fraction, so obtained, containing the acylated enzyme was scanned spectrophotometrically from 390 to 240 mμ, revealing an absorption at λ_{max} 326 mμ (log e=4.424). Comparison of the λ_{max} and log e_{max} of activated native trans-cinnamoyl papain to that of trans-cinnamoyl cysteine (the thiol ester model) and N-acetylserinamide (the hydroxyl ester model) as shown in Table II[13] below indicates λ_{max} of the thiol ester model to be closer to that observed for the acyl enzyme. Upon denaturation of trans-cinnamoyl papain in 4.8M guanidinium chloride λ_{max} shifts to 301-309 mμ which, as in hippuryl papain, is in good agreement with the acylated thiol model in a more uniform nonperturbed environment. Indication of the intermediacy of the observed species is provided by the following evidence: (1) A complete system showed an absorption at 350 mμ which first increased to a maximum and then decreased to zero. (2) The isolated species has the characteristic extinction of the trans-cinnamoyl moiety and a λ_{max} which differs from the reactant trans-cinnamoyl imidazole (λ_{max} 307 mμ) and the product trans-cinnamate ion (λ_{max} 269 mμ). (3) The trans-cinnamoyl moiety is not separated from the native or denatured enzyme on Sephadex filtration, implying covalent bonding. (4) Addition of the specific substrate, BAEE (shown in Figure I), to the trans-cinnamoyl enzyme showed that the rate of deacylation of the trans-cinnamoyl group was coincident with the rate at which papain catalyzed hydrolysis of the specific substrate reappears.[14] In the light of the kinetic evidence for BAEE hydrolysis involving a thiol group, (see section on kinetics) and the implication of a thiol group at the active site, Brubacker and Bender concluded that observation (4) implied a bonding of the trans-cinnamoyl moiety at the same active site, (probably the thiol group) responsible for BAEE hydrolysis.

Table II

Acyl Enzyme Models

trans-cinnamoyl derivative	λ_{max}(mμ)	log e_{max}(mμ)
papain	326	4.424
N-acetylserinamide	281.5	4.385
Cysteine	306	4.354

Also indicative of a covalent acyl enzyme intermediate was the work of Kirsch and Katchalski.[15] The investigators compared the enzyme catalyzed to hydroxide catalyzed ratio of the hydrolysis rate to the ^{18}O exchange rate of acyl-thiol

carbonyl labeled ^{18}O-ethyl hippurate (shown in Figure I). Assaying the remaining ester vs. time, they found a hydroxide ion catalyzed ratio of 14, but the enzyme catalyzed ratio of 80 was within experimental error of no detectable exchange. The authors concluded that the enzymatic pathway for hydrolysis either passes through an acyl enzyme intermediate or through an enzyme substrate complex, which hinders ^{18}O exchange sterically.

The further finding by Brubacher and Bender[13] that in the deacylation of trans-cinnamoyl papain in the presence of added nucleophiles, the rate of nucleophilic catalysis by amines was much greater than for the oxygen analogues, was taken by the authors to implicate a thiol ester as the enzyme intermediate.

ENZYME KINETICS

Papain has a broad specificity toward amides, and will hydrolyze a polypeptide more completely than either pepsin or trypsin.[4] Kinetic investigations of papain catalyzed hydrolysis have relied mainly upon synthetic substrates such as N-acyl α-amino derivatives of esters and amides of α-amino acids. Kinetic studies on these substrates have yielded much significant information as to the mechanism of catalysis.

Since Michaelis-Menton kinetic parameters have been employed throughout this paper, they are derived below assuming both the kinetic path shown and steady state conditions.

$$E + S \underset{k_{-a}}{\overset{k_a}{\rightleftharpoons}} ES \xrightarrow{k_b} E + P$$

$$0 = k_a(S)(E) - (k_{-a} + k_b)(ES)$$

$$(E_0) = (E) + (ES)$$ where (E) = concentration of free enzyme
(E_0) = enzyme added initially

$$\frac{dp}{dt} = \frac{k_b(E_0)(S)}{(S) + \frac{k_{-a} + k_b}{k_a}}$$

definitions: $k_{cat} = k_b$, $K_m = \frac{k_{-a} + k_b}{k_a}$, K_s = ES dissociation constant = $\frac{k_{-a}}{k_a}$

Smith and coworkers,[1] studying the pH and temperature dependencies of BAEE hydrolysis of the Michaelis Menton kinetic parameters, found k_{cat}/K_m to be a concave downward bell shaped curve as a function of pH. The limbs of the BAEE curve appear to represent the titration of two prototropic groups in the enzyme with pK_1=4.3 and pK_2=8.02 at 37°. The shift in the descending limb with temperature indicated a heat of ionization of 5.1 kcal/mole at 0°, which could correspond to either an α-amino or a thiol group in the opinion of the authors. They suggest the latter alternative due to the proven necessity of a free thiol group to enzyme activity. A lack of significant shift in pK_1 with temperature, implicated, to the authors, the titration of a carboxylate ion other than an α-carboxyl group, as shown by the negligible heat of ionization.

Although it was shown that positively charged substrates are hydrolyzed more readily than neutral ones, and that negatively charged substrates show inhibition, the shape of the k_{cat}/K_m vs. pH curves for basic BAEE, BAA (shown in Figure I), and neutral hippuramide were nearly identical, only the value of k_{cat}/K_m (lim) was greatly different. This indicated to the authors that acylation proceeded by the same mechanism in all of these cases (i.e., all dependent upon two prototropic groups). A plot of k_{cat} vs. pH for BAEE showed this rate constant to be pH independent down to pH 5.0. Below this value, a k_{cat} decrease was seen, which was

thought to be indicative of a single titratable group of pK_a 3.5 at 25°, active in the decomposition of an acyl intermediate to products. However, correcting Smith's pH-Stat data for the state of ionization of the product at low pH, Sluyterman[16] found no pH dependence. Williams[17] has also found no pH dependence in the hydrolysis of methyl hippurate.

In a study of papain catalyzed hydrolysis of a series of hippurate esters,[18] Lowe and Williams found that nine of the eleven esters studied have essentially the same value of k_{cat} ($2-4\ sec^{-1}$). Kirsch and Igelstrom[19] found similar k_{cat} independence of leaving group in a series of carbobenzoxyglycine esters. To account for this observation, in light of an acyl enzyme intermediate, Lowe and Williams proposed the following kinetic scheme (where k_2, k_3, P_1 and P_2 are the acylation rate constant, deacylation rate constant, an alcohol, and hippuric acid, respectively).

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ES \xrightarrow{k_2} \underset{\substack{+\\ P_1}}{ES'} \xrightarrow{k_3} E + P_2$$

assuming steady state conditions

$$\frac{dP_2}{dt} = \frac{\dfrac{k_2\,k_3}{k_2+k_3}\,(E_0)(S)}{(S) + \dfrac{k_3}{(k_2+k_3)}\,\dfrac{(k_{-1}+k_2)}{k_1}}$$

definitions: $k_{cat} = \dfrac{k_2\,k_3}{k_2+k_3}$, $K_m = \dfrac{k_3}{(k_2+k_3)}\,\dfrac{(k_{-1}+k_2)}{k_1}$, $k_{cat}/K_m = \dfrac{k_1k_2}{(k_{-1}+k_2)}$

in which $k_2 \gg k_3$ and therefore $k_{cat} = k_3$. According to these kinetics, if $k_{cat}/K_m = k_2/K_s$, then $k_2 \ll k_{-1}$. A plot of log (k_{cat}/K_m) vs. σ gave a good linear fit with $\rho = 1.2$, indicating, according to the authors, k_{cat}/K_m to be k_2/K_s where K_s is a constant and therefore $k_2 \ll k_{-1}$.

The functional dependence of the deacylation rate constant upon pH was determined by Brubacher and Bender[13] using the isolated trans-cinnamoylated papain added to the desired buffer solution, and the absorption of the difference spectrum at 330 mμ followed with time. The authors observed the deacylation rate constant (k_3) to increase in a sigmoid fashion with pH to a k_3 (lim) value of 3.68×10^{-3}. Deacylation was apparently dependent upon the ionization of a single prototropic group of pK_a 4.69, which the authors proposed to be a carboxyl group.

In a comparison of papain catalyzed BAA to BAEE hydrolysis, Whitaker and Bender[20] spectrophotometrically reinvestigated the kinetics of hydrolysis, extending the pH range employed by Smith and coworkers[1] and analyzing the kinetic data in terms of the rate constants and prototropic equilibria illustrated below by making

$$\begin{tikzcd}
EH_2 \arrow[d, shift left, "K_1"] \arrow[d, leftarrow, shift right] & EH_2S \arrow[d, shift left, "K_1"] \arrow[d, leftarrow, shift right] & EH_2S' \arrow[d, shift left, "K_1'"] \arrow[d, leftarrow, shift right] & \\
EH + S \arrow[r, shift left, "k_1(\mathrm{lim})"] \arrow[r, leftarrow, shift right, "k_{-1}"'] \arrow[d, shift left, "K_2"] \arrow[d, leftarrow, shift right] & EHS \arrow[r, "k_2(\mathrm{lim})"] \arrow[d, shift left, "K_2"] \arrow[d, leftarrow, shift right] & EHS' \arrow[r, "k_3(\mathrm{lim})"] & EH + P_2 \\
E & ES + P_1 & &
\end{tikzcd}$$

certain assumptions: (1) K_s is pH independent above pH 5.0, (2) BAA and BAEE share a common mechanistic pathway in their papain catalyzed hydrolysis, (3) k_3 is independent of pH at high pH, and (4) steady state conditions. The authors observed that although the k_{cat}/K_m vs. pH dependencies of BAA and BAEE are identical in form, the k_{cat} vs. pH dependencies of the two substrates are very different. They conclude from this, that granting assumption (2), two rate steps are involved in these hydrolyses, and of the two one is slower in amide hydrolysis whereas the other is slower in ester hydrolysis. A complete analysis in terms of the proposed rate

constants demonstrates the following: (1) a sigmoid dependence of k_3 to pH; (2) the pK_1' for BAEE deacylation is the same as that for BAA deacylation, which in conjunction with (1) supports assumption (3), and shows the dependence of deacylation upon a group of pK_a 3.91; (3) k_3 (lim) for both BAA and BAEE are equal within experimental error, which is to be expected for the deacylation of a common acyl moiety; (4) k_2 (lim) for BAEE is 3.2 fold greater than k_3 (lim); (5) k_3 (lim) for BAA is three fold greater than k_2 (lim); (6) the values of pK_1 and pK_2 for the acylation step of BAEE, 4.29 and 8.49 respectively, are essentially indentical to those for BAA, and similar to the values obtained earlier by Smith and coworkers.[1] Employing these values, internal consistency of the data to the proposed scheme of equation (2) was shown by using the derived values of the limiting rate constants, prototropic dissociation constants and the value of the substrate dissociation constant to calculate k_{cat}/K_m, k_{cat} and K_m vs. pH profiles which displayed good correspondence to the empirical data, except in the region below pH 4.5 in the K_m and k_{cat} vs. pH plots for BAA. Bender and Brubacher[21] offer an explanation for these discrepancies as perhaps representing either an increase in K_s with pH (in this range) due to the increased repulsion of the positively charged substrate by the progressively more positively charged enzyme, or a perturbation of the enzyme of such a nature as to shift the pK_1 of the enzyme substrate complex below the pK_1 of the free enzyme.

In conflict with the bell shaped pH dependencies of k_{cat} obtained by Whitaker and Bender,[20] Sluyterman[26] and Williams[17] both reported that k_{cat} was pH independent for ethyl hippurate hydrolysis down to pH 4.2 and 3.8 respectively. Lowe and Williams[31] suggest that the pH dependence of deacylation in benzoylargininyl papain is due simply to binding of the positively charged guanido group by a carboxylate ion, assisting deacylation by orienting the thiol ester bond and perhaps modifying the conformation of the acyl enzyme. They note that although the k_3 of benzoylargininyl papain is 7 times greater than k_{cat} of ethyl hippurate (taken as $k_{deacylation}$) at pH 6.0, the former is approximately equal to the latter at pH 3.0, where the carboxyl group is largely protonated. This hypothesis would predict that the masking of the basic group (e.g., with a N-formyl group) should reduce k_{cat} (lim) to the area of 2.7 sec^{-1} (the k_{cat} of ethyl hippurate). The recent work by Bender and Brubacher[21] has shown that for Z-L-lysine p-nitrophenyl ester (shown in Figure I), the value of k_{cat} (lim) drops from 45 sec^{-1} to 32 sec^{-1}. The authors consider these two values to be the same. Furthermore, substitution of BCME (shown in Figure I) for BAEE, (which provides a substrate with an isosteric acyl function), has been recently found by Cohen and Petra[23] to exhibit no effect (20.2 vs. 20.15 sec^{-1}) on k_3 (lim) calculated similarly. The latter results imply that the presence of a positive charge on the substrate does not increase the deacylation rate.

Kinetic studies by Bender and Brubacher[21] with the series p-nitrophenyl, benzyl and methyl Z-L-lysine esters as a function of pH, analyzed in terms of the scheme of equation (2), similar to the treatment of Whitaker and Bender,[20] have followed similar k_{cat}, k_{cat}/K_m, and K_m vs. pH dependencies to those shown by BAEE. For this series of esters, k_3 was in all cases at least 3.5 fold smaller than k_2. However, it was found that K_s decreased from a value of 10.7mM for the methyl ester to approximately 0.033mM for the p-nitrophenyl ester, a 3.2×10^2 fold drop. The authors state that a change in K_s of this magnitude strongly implies that the substrate leaving group is bound at some enzymatic site. This dependence of K_s upon the structure of P_1 is in conflict with the conclusion of Lowe and Williams[18] based upon the linear dependence of log (k_{cat}/K_m) vs. σ for four aryl hippurate esters.

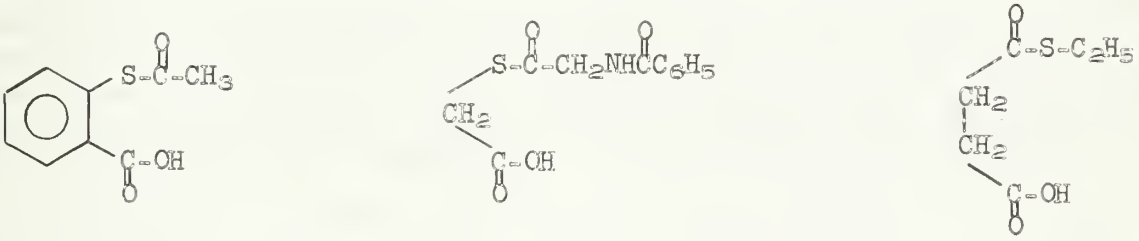
MECHANISITIC PROPOSALS

Several mechanisms have been proposed in the course of papain investigations in order to explain some of the experimental observations. Most of those proposed agree that an acyl enzyme is formed, which is later deacylated by various means. Lowe and

Williams[18] based their suggestion that the k_2 step is subject to nucleophilic catalysis combined with acid catalysis on the observations that (1) for substituted aryl hippurate esters log (k_{cat}/K_m) gives a better fit to σ than to σ^- $(\rho=1.2)$ indicating relative insensitivity in k_2 and (2) for BAA hydrolysis the data of Smith and coworkers[1] show $k_{cat(H_2O)}/k_{cat(D_2O)}$ to be 0.8, which Lowe and Williams consider to be an indication of acid catalyzed ester hydrolysis. It is their view that the alkaline limb of the k_{cat}/K_m vs. pH curve represents not thiol, but imidazolium titration (for histidine $pK_a = 5.6-7.0$ at 25°, $\Delta H = 6.9-7.5$ kcal/mole). Their proposal, then, is that the thiol group is acylated by proton abstraction from a sulfhydryl group by a carboxylate ion with sulfur attack at the acyl moiety and proton donation to the leaving group by imidazole. It should be noted that there are only two histidine residues in papain, at 106 and 175. Further, the direct evidence for imidazole implication (it is bound by carboxymethylation with irreversible inhibition)[24] has not been observed by other workers[25,26] who have found that only cysteine is bound by carboxymethylation.

Whitaker and Bender[20] employed k_{cat} as a measure of k_2 in the hydrolysis of BAA and reported $k_{H_2O}/k_{D_2O} = 1.35$. They clearly expected a larger value in accordance with general base catalysis, but this low value lends no support to such catalysis. The authors suggest that the carboxylate ion acts as a base and the thiol group as an acid which is acylated in the k_2 step.

A mechanism for the deacylation reaction offered by Smith[1] involved carboxylate attack on the thiol ester intermediate. Lowe and Williams[22] tested this proposal for nucleophic carboxylate catalysis on the ester by comparing intramolecularly catalyzed hydrolysis rates and activation parameters of some appropriate models shown in Figure II with the k_{cat} and activation parameters calculated from the temperature dependency of k_{cat} (from four points) for methyl hippurate hydrolysis. The rate constants for the hydrolysis of II and III are measured from the pH independent region of k_{obs} vs. pH. The best model of hippuryl papain (II) is 3×10^{-5} fold slower than the k_{cat} for the enzyme catalyzed hydrolysis. The other models are also 10^{-5} fold slower. Activation parameter comparison for III shows that the entropy of activation for the enzymic k_{cat} is 20 e.u./mole lower than the model, but the enthalpy of activation is nearly 7 kcal/mole lower for the enzymic reaction then the model. The authors conclude that the large difference in rate constants suggests that nucleophilic catalysis of deacylation by a carboxylate ion is unlikely.



I II III

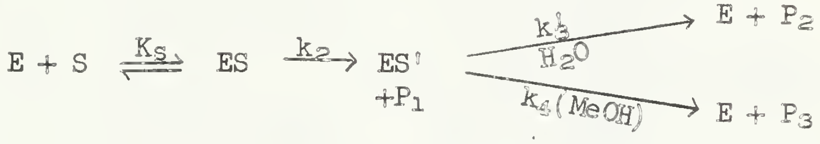
Figure II. Models of the acyl enzyme

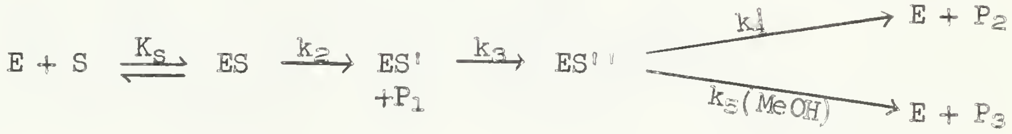
Lowe and Williams[31] proposed that deacylation is catalyzed by nucleophilic imidazole catalysis at the thiol ester followed by a rapid hydrolysis step. Kinetic support for imidazole participation in deacylation has come only from the results of Cohen and Petra[23] on α-N-benzoyl-L-citrulline methyl ester, where a sigmoid dependence of k_3 upon pH with a pK_a of 7 was calculated. The form of this dependence implies the catalytic group is active in the protonated form.

The observation of large deuterium isotope effects by Whitaker and Bender,[20]

$k_{cat_{H_2O}}/k_{cat_{D_2O}} = 2.45$ for BAEE hydrolysis, and Brubacher and Bender,[12,22] $k_{H_2O}/k_{D_2O} = 3.35$ for deacylation of trans-cinnamoyl papain, all support general base catalysis on the thiol ester by a carboxylate ion as the mechanism of the deacylation step by implying proton transfer in the transition state of this step. The complicity of a carboxylate ion to deacylation has been discussed above. In a study of the deacylation of trans-cinnamoyl papain by added amine nucleophiles, Brubacher and Bender[13] observed that a plot of log $k_{\text{amine cat. deacylation}}$ (i.e., log k_4) vs. pK_a of the amine produced no correlation to any simple relationship. A plot of the observed deacylation rate constant $k_{obs} = k_3 + k_4$ (added nucleophile) vs. the added nucleophile concentration gave a straight line with no evidence of binding of the nucleophile. The authors, however, felt that certain comparisons of k_4 for appropriate nucleophiles of similiar pK_a or structure necessitated that a specific binding interaction exists, and that basicity has little, if any, influence upon k_4. The authors considered this supportive evidence for general base catalysis in the deacylation of trans-cinnamoyl papain. They reasoned that the less basic the nucleophile, the more readily it will release its proton, but the more basic the nucleophile, the better, so that these two effects would tend to cancel. In regard to the general applicability of these observations, it must be noted that, both the added nucleophile effects and the largest observed deacylation isotope effects were observed in trans-cinnamoyl papain hydrolysis, where k_3 (lim) = 3.68×10^{-3} sec^{-1}, or 700 fold smaller than the k_{cat} for methyl hippurate hydrolysis, and about 10,000 fold smaller than N-benzoylargininyl papain deacylation. Lake and Lowe[27] have interpreted this as indicative of either the involvement of a different rate determining step, or the employment of another mechanism in the hydrolysis of this nonspecific trans-cinnamoyl papain. They have also found $k_{3_{H_2O}}/k_{3_{D_2O}}$ for p-nitrophenyl hippurate to be 1.7, which they have interpreted as a secondary isotope effect.

A fourth deacylation pathway has been recently proposed by Lake and Lowe[27] as involving a slow conformational change from the acyl thiol enzyme (ES') to a conformer (ES''), in comparison to the relatively rapid subsequent breakdown step giving product. To test the pathway involved in general base catalysis (Scheme I) against this fourth proposal (Scheme II), the authors studied the effect of added methanol upon k_{cat} for the production of P_1 from p-nitrophenyl hippurate, and also for the production of hippuric acid (P_2) from methyl hippurate. The k_{cat} for product formation, according to each scheme, is the following: for P_1 in Scheme I

Scheme I


Scheme II


(assuming $k_2 \gg k_3' + k_4$ (MeOH)) $k_{cat} = k_3' + k_4$ (MeOH), in Scheme II (assuming $k_2 \gg k_3$ and $k_3 \ll k_4' + k_5$ (MeOH)) $k_{cat} = k_3$; for P_2 in Scheme I (assuming $k_2 > k_3' + k_4$ (MeOH)) $1/k_{cat} = 1/k_3'$, and in Scheme II (assuming $k_3 \ll k_4' + k_5$ (MeOH)) $1/k_{cat} = (k_2 + k_3)/k_2k_3 + (k_2 + k_3)(k_5\ (MeOH)/k_2k_3k_4'$. It was observed for p-nitrophenol (P_1) that k_{cat} was independent of the methanol concentration up to 2M methanol, and

decreased slightly above this point. Following hippuric acid production, $1/k_{cat}$ was seen to be linearly related to the methanol concentration. These results are in agreement with any pathway of the kinetic form of Scheme II with $k_3 \ll k'_4 + k_5$ (MeOH), but do not provide a description of the k_3 step. Lake and Lowe state that these observations provide strong support for the absence of general base catalysis in the deacylation of hippuryl papain.

SUMMARY

A large collection of experimental evidence has accumulated to specify certain aspects of the pathway of papain catalyzed hydrolysis of synthetic substrates. Although the evidence supporting an acyl thio-enzyme is significant, the detailed mechanism of its formation and deacylation is subject to the uncertainty of conflicting observations and interpretations. Particularly evident, has been the dependence of the observations and hence the proposed mechanism, upon the substrate employed. It would appear that to make any generalized statement as to the nature of papain catalyzed hydrolysis would at this point be premature due to a lack of knowledge concerning possible variations or discontinuities in the mechanism with a spectrum of substrates.

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THE PHOTOSENSITIZED CIS-TRANS ISOMERIZATION OF OLEFINS

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The light induced cis-trans isomerization of olefins has long been known, and has been widely used as a synthetic tool, especially for the preparation of the less stable member of an isomeric pair of olefins. It has only been within recent years, however, that the mechanisms of these isomerizations, particularly those occurring under triplet photosensitized (hereafter referred to as photosensitized) conditions, have been intensively studied. This seminar will be specifically concerned with mechanistic aspects of the photosensitized cis-trans isomerization of olefins occurring in solution, the area of vapor phase photosensitized isomerizations having recently been reviewed.[1] The utility of such studies in enhancing understanding of photochemical processes in general, and triplet energy transfer[2] in particular, will also be emphasized.

NON-CONJUGATED OLEFINS

Theoretical calculations[1,3] indicate the most stable configuration of the lowest triplet state of ethylene and other non-conjugated olefins to be the twisted, non-spectroscopic form (the so-called phantom triplet,[9] p) in which the planes defined by the two CH_2 groups are orthogonal thus minimizing interaction between the two $2Cp_z$ orbitals and electrons.

Such a twisted triplet state provides a ready pathway for the cis-trans isomerization of simple olefins, as formation of this triplet from either a cis or trans olefin is expected to result in decay (via twisting and intersystem crossing) to both the cis and trans isomers. The existence of a twisted triplet as a common intermediate in these isomerizations is based both on theoretical predictions,[1,3,4] and on the finding that the sum of the quantum yields for the cis to trans (Φ_{tc}) and trans to cis (Φ_{tc}) photosensitized isomerization of many olefins, in which the olefin triplet is formed with unit quantum efficiency, is one.[5] Calculations[6] indicate that $\Phi_{ct} + \Phi_{tc}$ equals one only if isomerization occurs solely from a common twisted triplet. If, however, isomerization occurs from two non-interconvertible spectroscopic triplets, $0 < \Phi_{ct} + \Phi_{tc} < 2$. The fact that $\Phi_{ct} + \Phi_{tc}$ has been found to equal but never to exceed one is strong presumptive evidence for a common-intermediate process.

Two types of triplet energy transfer processes, vertical and non-vertical, can, in principle, occur via a coupled energy transfer process[2] of the form shown in eq 1, S^{T^1} being the triplet energy donor (sensitizer), and A^{S^0} being the (olefin) acceptor. Vertical (classical) energy transfer occurs in accordance with the Franck-Condon principle,[7] producing vibrationally excited, spectroscopic olefin triplets which then relax vibrationally (via twisting) to the twisted triplet with subsequent decay to the isomeric ground state olefins. Non-vertical (non-classical) energy transfer[4,8,9] directly to the twisted triplet, although forbidden by the Franck-Condon principle for radiative processes, can occur in a coupled triplet energy transfer process. Vertical and non-vertical energy transfer are competitive processes, the less probable and hence less efficient non-vertical process being unimportant relative to the vertical process when the triplet energy of the sensitizer, E_T^S (measured by the 0-0 band) exceeds the triplet energy of the acceptor, E_T^A, by ~3 or more kcal/mole. In such a case vertical energy transfer is diffusion-controlled,[2] occurring on every collision. When E_T^S is less than E_T^A the classical energy transfer process is endothermic.

(1) $$S^{T^1} + A^{S^0} \longrightarrow S^{S^0} + A^{T^1}$$

Non-vertical energy transfer can now effectively compete with the vertical process which, although intrinsically more efficient, has a higher activation energy than the non-vertical process. When energy transfer is endothermic and hence not diffusion-controlled, the time required for this process to occur has been calculated to be at least 10^{-8} sec.[9a] It is thus not surprising that the lower energy non-vertical transitions can occur, as the time required for radiative transitions, for which the Franck-Condon principle was formulated, is about 10^{-15} sec. Little is known about the detailed nature of non-vertical processes, however, which will be discussed further in connection with the cis-trans isomerization of the stilbenes.

The acetone sensitized cis-trans isomerization of 2-pentene has been studied in detail in a variety of solvents by Borkman and Kearns.[10] These workers found that for concentrations of 2-pentene greater than 1.0 M, $\Phi_{ct} + \Phi_{tc}$ equalled 1.0 ± 0.1 in accord with isomerization via a common, twisted triplet intermediate. The quantum yield for energy transfer from acetone to 2-pentene was determined to be 1.0 ± 0.1 indicating that every acetone triplet eventually transfers its excitation energy to a 2-pentene molecule; this finding implies nothing about the efficiency of energy transfer during a single collision, however.

It was found that although 2-pentene completely quenches the phosphorescence of acetone, it does not affect the fluorescence of acetone under the same conditions in which the acetone sensitized 2-pentene isomerization occurs with 100% efficiency, indicating that energy transfer from acetone to 2-pentene is not vibrational in nature and proceeds from the triplet state of acetone ($\tau \sim 10^{-6}$ sec) rather than from the shorter-lived singlet state ($\tau \sim 2.5 \times 10^{-8}$ sec), a fact which has long been assumed in ketone photosensitized olefin isomerizations, but never before rigorously proven. Although attempts to detect 2-pentene triplets spectroscopically (e.g., by esr in rigid glasses at 77° K) under conditions of the isomerization were unsuccessful, perhaps owing to a short triplet lifetime, it is quite likely that, in accord with the Wigner spin conservation rule, it is the 2-pentene triplet which is formed upon energy transfer.

From a study of the initial rate of the isomerization as a function of the concentration of 2-pentene, Borkman and Kearns were able to calculate the quenching constant, K_s, for the triplet energy transfer process, where $K_s = \tau_T k_t$, τ_T being the acetone triplet lifetime in solution and k_t being the overall bimolecular rate constant for energy transfer from the acetone triplet to 2-pentene. From the experimentally determined value of K_s, k_t was calculated to be $\sim 10^7$ M^{-1} sec^{-1}, a value about 10^3 times less than the theoretically predicted diffusion-controlled one. This finding led Borkman and Kearns to conclude that the energy transfer step, known to involve close contact between sensitizer triplet and acceptor,[2] is best written as two distinct steps (eq 2), $[S^{T^1} \cdots \text{olefin}^{S^0}]$ being a collision complex

$$(2) \qquad S^{T^1} + \text{olefin}^{S^0} \underset{k_b}{\overset{k_a}{\rightleftharpoons}} [S^{T^1} \cdots \text{olefin}^{S^0}] \xrightarrow{k_c} S^{S^0} + \text{olefin}^{T^1}$$

in which 2-pentene is adjacent to the acetone triplet but in which energy transfer has not yet occurred; this collision complex can revert back to 2-pentene without energy transfer (k_b) or undergo dissociation with concurrent energy transfer (k_c). Kinetic analysis of eq 2 indicates that $k_t = k_a k_c/(k_c + k_b)$. If k_c, the nearest neighbor rate of energy transfer, is large compared with k_b then $k_t = k_a$, i.e., the process is diffusion-controlled. If $k_c \ll k_b$ then $k_t = k_c k_a/k_b$ and k_t is less than diffusion-controlled as found for 2-pentene. Furthermore if it is assumed that the collision complex has negligible stability, i.e., ΔH^0 of formation ~ 0,

then k_a/k_b should be temperature independent indicating that k_t will be a function of temperature only if k_c is. Variable-temperature kinetic studies in the 25° to -78° range did indicate a temperature dependence in k_t (k_c) from which an activation energy of ~ 4.3 kcal/mole was calculated for the energy transfer step.

The E_T of acetone has been estimated from phosphorescence studies to be ~ 80 kcal/mole[10] (a value disputed by Cundall[11] who claims a value of ~ 75 kcal/mole), whereas the 0-0 triplet energy of 2-pentene has been taken by Kearns to be equal to that of ethylene,[4] ~ 82 kcal/mole (a value which may be slightly too high[11]). Triplet energy transfer from acetone to 2-pentene is thus predicted to be endothermic by ~ 2 kcal/mole, in reasonably good agreement with the experimentally determined activation energy, thus accounting for the observed rate of energy transfer.

Morrison, et. al., have used the photosensitized cis-trans isomerization of olefins as a tool to investigate intramolecular triplet energy transfer,[12] i.e., light absorbed in one part of a molecule results in a chemical reaction at another, non-conjugated part of the same molecule via energy transfer from the initially excited chromophore to the reacting center.

The most conclusive evidence for intramolecular triplet energy transfer comes from a study of the irradiation of trans- and cis-1-phenyl-2-butene,[12b-d] light of 230-280 mμ being used to insure that only the phenyl chromophore is excited to the π,π^* triplet state; the only observable reaction was cis-trans isomerization with $\Phi_{ct}=\Phi_{tc}=0.21 \pm 0.016$. The mechanism suggested by Morrison for this photoisomerization is given in eqs 3-6.[12c,d] It is assumed that the phenyl donor

$$(3)\qquad \underline{t}S^0 \xrightarrow{h\nu} \underline{t}S^1 \xrightarrow{k_D} \underline{t}S^0;\quad \underline{c}S^0 \xrightarrow{h\nu} \underline{c}S^1 \xrightarrow{k_D} \underline{c}S^0$$

$$(4)\qquad \underline{c}S^1 \xrightarrow{k_{IC}} \underline{c}T^1 \xrightarrow{k_1} p \qquad\qquad (5)\qquad \underline{t}S^1 \xrightarrow{k_{IC}} \underline{t}T^1 \xrightarrow{k_2} p$$

$$(6)\qquad \underline{t}S^0 \xleftarrow{k_3} p \xrightarrow{k_4} \underline{c}S^0$$

and double bond acceptor chromophores are non-interacting in the ground and singlet excited states, and also that the rates of intersystem crossing (k_{IC}) and radiationless decay (k_D) of the phenyl donor are the same for either isomer; k_1 and k_2 are the rates of energy transfer from the phenyl triplet to the cis and trans olefinic linkage, respectively, giving a common, twisted triplet, p. Since $E_T^{C_6H_5-}$ (~ 85 kcal/mole) is at least 2-3 kcal/mole greater than the 0-0 triplet excitation energy of either isomer, $k_1=k_2$ and energy transfer probably occurs at close to the diffusion-controlled rate to give vibrationally excited, spectroscopic olefinic triplets which decay to p which undergoes subsequent decay with concomitant cis-trans isomerization (k_3,k_4).

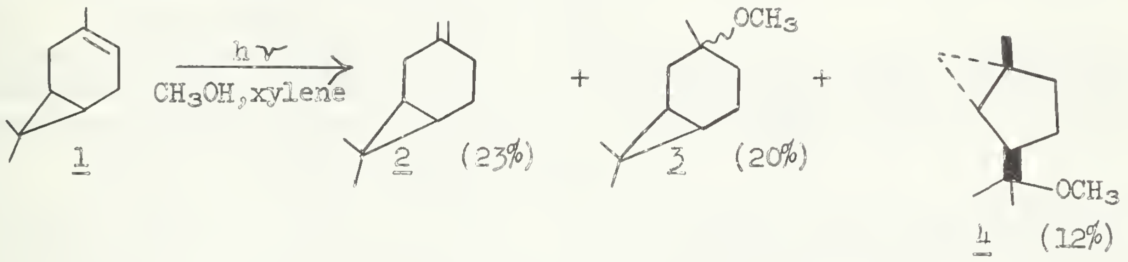
Kinetic analysis of eqs 3-6 leads to the prediction that the photostationary state composition, $(\text{cis})_s/(\text{trans})_s$, is equal to $(k_2/k_1)\cdot(k_4/k_3)$. Since $k_1=k_2$, $(\text{cis})_s/(\text{trans})_s=k_4/k_3$, i.e., the photostationary state composition is determined by the decay ratio of p, an intrinsic property of the excited state in a given solvent at a given temperature.[16] Moreover, this expression predicts that excitation of the double bond by intermolecular energy transfer from benzene should lead to the same $(\text{cis})_s/(\text{trans})_s$ as the intramolecular process; in accordance with this prediction, $(\text{cis})_s/(\text{trans})_s$ was found to equal 1.0 for both types of sensitization processes.

Evidence that the observed intramolecular energy transfer is electronic and not vibrational, *i.e.*, from a vibrationally excited ground state of the phenyl group leading to thermal *cis*-*trans* isomerization, comes from the observation that the quantum yield for the *trans* to *cis* isomerization in cyclopentane is reduced from 0.21 to 0.15 in the presence of an equimolar amount of the triplet quencher *trans*-2-hexene, indirectly indicating that intramolecular transfer of electronic energy does occur.

Cis-*trans* isomerizations have also been observed to occur upon irradiation of *trans*-4-hexen-2-one[12a] and *trans*-5-hepten-2-one.[12b] Formation of the *cis* isomer upon excitation of the carbonyl group of *trans*-5-hepten-2-one was taken by Morrison as fairly good evidence for intramolecular energy transfer from the carbonyl triplet to the double bond, although the possibility of vibrational energy transfer was not ruled out. The situation with regard to the isomerization of *trans*-4-hexen-2-one is unclear, products arising from acetyl and 2-butenyl radicals being observed.

Recent studies of the benzene, toluene and xylene sensitized irradiation of a series of 1-alkylcycloalkenes have indicated the possible formation of the highly strained *trans* isomers.[13] Irradiation of (+)-3-carene (1) was found to give (+)-3(10)-carene (2); in the presence of methanol, ethers 3 and 4 were also formed (eq 7). Deuterium labeling studies indicated the rearrangement to the exocyclic olefin to be intermolecular with respect to the proton shift.

(7)



These observations of proton incorporation, ether formation, rearrangement and Markovnikov addition are suggestive of ionic processes, and led Kropp to suggest that decay of the twisted cycloalkene triplet, formed *via* triplet energy transfer, leads to both *cis* and *trans* olefin, the highly strained *trans* isomer undergoing protonation with relief of strain to give a carbonium ion which leads to the observed products.[13a] The presence of olefin triplets in these reactions was suggested by the finding of Carroll and Marshall that the reaction rate is decreased by added oxygen.[13b] These workers propose a mechanism involving direct protonation of the olefin triplet to give a carbonium ion and the observed products. Kropp believes this mechanism to be less likely in view of the finding that exocyclic and acyclic olefins, the *trans* isomers of which are not highly strained, undergo neither photoinduced double bond migration nor ether formation.

Other examples of photosensitized *cis*-*trans* isomerizations of simple olefins include the isomerization of *cis*, *trans*, *trans*-1,5,9-cyclododecatriene to the *cis*, *cis*, *trans* and *trans*, *trans*, *trans* isomers,[14] and the isomerization of methyl oleate to methyl elaidate.[15]

CONJUGATED OLEFINS

The photosensitized *cis*-*trans* isomerization of the stilbenes and 1,2-diphenylpropenes in benzene solution has been studied in considerable detail,[16-20] and will be discussed with particular reference to the stilbenes, the results obtained for the 1,2-diphenylpropenes being similar except when otherwise noted.

The mechanism represented by eqs 8-12 will serve as a starting point for discussion of the isomerization. In this mechanism only vertical energy transfer

(8) $$S^{S^0} \xrightarrow{h\nu} S^{S^1} \xrightarrow{k_{IC}} S^{T^1}$$

(9) $$S^{T^1} + \underline{t}^{S^0} \xrightarrow{k_1} \underline{t}^{T^1} + S^{S^0}$$ (10) $$S^{T^1} + \underline{c}^{S^0} \xrightarrow{k_2} \underline{c}^{T^1} + S^{S^0}$$

(11) $$\underline{c}^{T^1} \longrightarrow \underline{t}^{T^1}$$ (12) $$(a)\ \underline{t}^{S^0} \xleftarrow{k_3} \underline{t}^{T^1} \xrightarrow{k_4} \underline{c}^{S^0}\ (b)$$

to cis- and trans-stilbene yielding the planar, spectroscopic transoid ($\underline{t}^{T^1}$) and cisoid ($\underline{c}^{T^1}$) triplets is proposed; conversion of $\underline{c}^{T^1}$ to $\underline{t}^{T^1}$ (eq 11) has been shown to occur as will be seen shortly. Eq 12b, decay of $\underline{t}^{T^1}$ to cis-stilbene, is a non-vertical, radiationless decay process[9a] completely analogous to the non-vertical excitation processes previously discussed; its importance will be assayed later. The light used was filtered to avoid direct excitation of either of the stilbene isomers, and no indication of any singlet state reaction of the stilbenes (e.g., phenanthrene formation) was found.[16] Furthermore, for high-energy sensitizers, i.e., $E_T^S >$ vertical excitation energy of either stilbene isomer by at least 3-5 kcal/mole, radiationless decay of S^{T^1} was found to be negligible, deactivation of S^{T^1} occurring only via energy transfer to the stilbenes.

Kinetic analysis of eqs 8-12 leads to the expression for the photostationary state composition given by eq 13. For high-energy sensitizers k_1 and k_2 will be

(13) $$(\underline{cis})_s/(\underline{trans})_s = (k_1/k_2)\cdot(k_4/k_3)$$

equal and diffusion-controlled, and the photostationary state composition will be constant, being determined solely by the decay ratio, k_4/k_3. Under such conditions the quantum yields are related to $(\underline{cis})_s/(\underline{trans})_s$ by eq 14. The 0-0 triplet

(14) $$\phi_{tc}/\phi_{ct} = k_4/k_3 = (\underline{cis})_s/(\underline{trans})_s$$

excitation energies of the stilbenes are ~57 kcal/mole for the cis isomer[21a,b] and ~50 kcal/mole for the trans isomer.[21b] As E_T^S approaches and falls below 57 kcal/mole, k_2 is predicted to decrease below the diffusion-controlled limit, k_1 remaining constant, thus leading to an increasingly cis-rich photostationary state. As E_T^S approaches and falls below 50 kcal/mole k_1 should also decrease. Below 50 kcal/mole the excitation ratio k_1/k_2 for the endothermic energy transfer process is predicted to become constant, being determined solely by the difference in the 0-0 triplet energies of the two isomers, i. e., $k_1/k_2 = \exp+[(E_T^c - E_T^t)/RT]$ $\sim 6 \times 10^6$ at 25°. This predicts a limiting photostationary state of essentially pure cis-stilbene.

The experimentally determined variation of the photostationary state composition,[8,16] extrapolated to infinite dilution with respect to the sensitizer concentration, with E_T^S for the stilbenes, fig 1, does not completely follow these predictions, however. The predicted high-energy region of constant photostationary state and subsequent increase in % cis-stilbene as E_T^S decreases below ~62 kcal/mole are observed; the other predictions are incorrect. With low-energy sensitizers ($E_T^S <$ ~62 kcal/mole) the value of k_2 (cis-stilbene excitation) falls off much more slowly than predicted, a finding which led Hammond to propose that triplet energy transfer to cis-stilbene occurs via non-vertical excitation

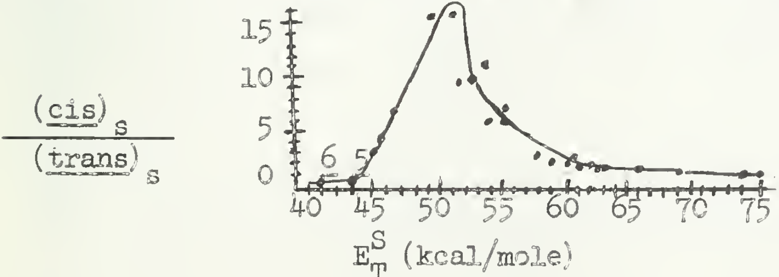


fig 1

with synchronous distortion to give the twisted phantom triplet (p) and/or $\underline{t}^{T^1}$, processes requiring less energy than transition to $\underline{c}^{T^1}$; since *trans*-stilbene is more stable than *cis*-stilbene by ~6 kcal/mole,[22] non-vertical excitation of the *cis* isomer to p or $\underline{t}^{T^1}$ should only become endothermic when $E_T^S < \sim 44$ kcal/mole in agreement with variable-temperature kinetic studies[16] which indicated no activation energy for this process in the 53-60 kcal/mole range. Inclusion of eq 15 in the kinetic scheme leads to the photostationary state composition given by eq 16. For high-energy sensitizers $k_1 = k_2 \gg k_5$ and eq 16 reduces to eq 13. Below ~62

(15) $S^{T^1} + \underline{c}^{S^0} \xrightarrow{k_5} \underline{t}^{T^1}, p + S^{S^0}$ (16) $(\underline{cis})_s/(\underline{trans})_s = k_1k_4/(k_2 + k_5)k_3$

kcal/mole k_2 decreases, k_1 and k_3 remaining constant in accord with the observed increase in $(\underline{cis})_s/(\underline{trans})_s$. Below ~51-52 kcal/mole, k_1 also decreases sharply, k_3 remaining essentially constant; $k_1/(k_2 + k_5)$ thus decreases explaining the general shape of fig 1 in the 45-50 kcal/mole region.

It is observed from fig 1 that the low-energy sensitizers eosin (5) and 9,10-dibromoanthracene (6) establish a photostationary state of essentially pure *trans*-stilbene; recent studies[18] have shown that photolysis of these sensitizers produces bromine atoms which cause thermal equilibration of the stilbenes.[1]

Sensitizers of $E_T^S < 53$ kcal/mole were found to give pronounced concentration effects in the photostationary state composition, $(\underline{cis})_s/(\underline{trans})_s$ decreasing as the concentration of the sensitizer increased; this finding was attributed to reversible energy transfer to *trans*-stilbene (eq 17).[16] Replacement of eq 9 by eq 17 in the kinetic scheme leads to eq 18 which is fit by the experimental data.

(17) $\underline{t}^{S^0} + S^{T^1} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \underline{t}^{T^1} + S^{S^0}$ (18) $(\underline{cis})_s/(\underline{trans})_s = k_1k_4/(k_2+k_5)(k_3+k_{-1}[S^{S^0}])$

In further accord with this idea of reversible energy transfer to $\underline{t}^{T^1}$, it was found that inclusion of the triplet quencher azulene, az (E_T ~29-42 kcal/mole) in the reaction mixture also gave photostationary states richer in *trans*-stilbene indicating eq 19 to be operative. The effect of added azulene was the same for all sensitizers used. Further evidence for quenching of $\underline{t}^{T^1}$ comes from examination of the Φ_{tc}/Φ_{ct} ratio obtained for high-energy sensitizers. While eq 14 was found to hold for the 1,2-diphenylpropene isomerization, it was not satisfied by the stilbenes. This deviation from eq 14 was found to be due, at least in part, to the existence of self-quenching of $\underline{t}^{T^1}$ (eq 20).[16]

(19) $\underline{t}^{T^1} + az^{S^0} \longrightarrow \underline{t}^{S^0} + az^{T^1}$ (20) $\underline{t}^{T^1} + \underline{t}^{S^0} \longrightarrow 2\underline{t}^{S^0}$

These quenching studies indicate that energy transfer to *cis*- or *trans*-stilbene leads to the ultimate production of the same triplet species which is then quenched to give *trans*-stilbene, *i. e.*, energy transfer to *cis*-stilbene produces a triplet which can be deactivated to *trans*-stilbene by quenching. However, quenching of $\underline{c}^{T^1}$ could not be detected. To explain these findings, Hammond postulated the rapid, irreversible decay of $\underline{c}^{T^1}$ to $\underline{t}^{T^1}$ (eq 11); this interconversion probably occurs *via* p, believed to be in equilibrium with $\underline{t}^{T^1}$ (eq 21). These

(21) $\underline{c}^{T^1} \longrightarrow p \rightleftharpoons \underline{t}^{T^1}$

findings are also evidence for the production of an electronically excited triplet(s) upon sensitization of *cis*-stilbene by low-energy sensitizers indicating that non-vertical energy transfer does not involve transfer of vibrational energy. Quenching effects were not observed for the 1,2-diphenylpropene system, indicating that conversion of both the *transoid* and *cisoid* triplets to p is rapid and irreversible, isomerization occurring only from p.[16]

Recent studies by Hammond and Herkstroeter have provided direct evidence as to the

nature of the energy transfer processes.[19] These workers used flash spectroscopy to study the rate of decay of various sensitizer triplets using *cis*- and *trans*-stilbene and 1,2-diphenylpropene as quenchers. Attempted direct study of the stilbene and 1,2-diphenylpropene triplets was unsuccessful due to their short lifetimes. From these quenching studies the rates of energy transfer, k_{ET}, from the sensitizer triplets to the olefin acceptors were determined. The results obtained confirm what has already been said about the nature of the energy transfer processes. Classically, if E_T^S is less than E_T^A, energy transfer will require an activation energy equal to $E_T^A - E_T^S$, the decrease in transfer efficiency as a function of E_T^S being given by eq 22.

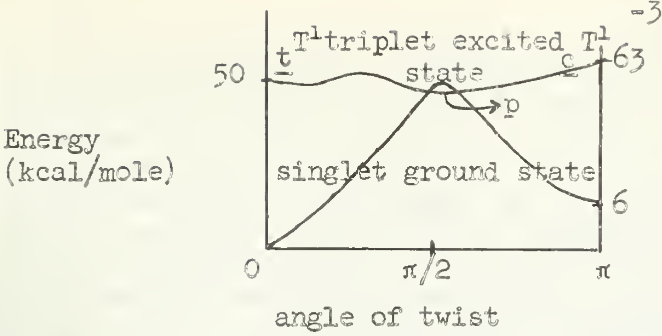
(22) $d(\log k_{ET})/d(E_T^S) = + 1/2.303\ RT$

The experimentally observed quenching curve for *trans*-stilbene had the slope indicated by eq 22 for sensitizers of $E_T^S \leq 48$ kcal/mole, indicating that non-vertical excitation of *trans*-stilbene to p does not occur. The behavior of *cis*-stilbene towards sensitizers of $E_T^S = 42$-58 kcal/mole did not fit eq 22, excitation of *cis*-stilbene being quite efficient even for sensitizers of E_T^S 10 kcal/mole too low to effect vertical excitation, in agreement with the postulated non-vertical process. As also inferred from photostationary state studies, neither *cis*- nor *trans*-1,2-diphenylpropene was found to exhibit classical behavior as a triplet quencher indicating that both of these isomers undergo efficient non-vertical excitation.

From these studies it was concluded that *trans*-stilbene can find no excitation pathway of substantially lower energy requirement than vertical excitation to $\underline{t}^{T^1}$, indicating p to be close to isoenergetic with $\underline{t}^{T^1}$ but below $\underline{c}^{T^1}$ in energy. Since neither of the 1,2-diphenylpropenes behaves classically, both the *cis* and *trans* isomers are apparently able to undergo transitions to one or more twisted states of lower energy than either the planar *cisoid* or *transoid* triplets. This is probably a consequence of the relief (*via* twisting) of the steric strain that exists in both the *cisoid* and *transoid* triplets owing to nonbonded interaction between a phenyl group and the phenyl or methyl group *cis* to it.

The results of the quenching studies as well as the observed non-vertical energy transfer to *cis*-stilbene may be explained either by the assumption that the two triplets, $\underline{t}^{T^1}$ and p, are in equilibrium (eq 21), or that only a single triplet, $\underline{t}^{T^1}$, exists, non-vertical excitation of *cis*-stilbene giving only $\underline{t}^{T^1}$. The latter hypothesis, although not rigorously disproven, appears to be much less likely. In order to accommodate this hypothesis it must be assumed that whereas $\underline{t}^{T^1}$ is selectively deactivated to *trans*-stilbene in quenching reactions, spontaneous decay of $\underline{t}^{T^1}$ yields both *cis*- and *trans*-stilbene. Furthermore, inclusion of p in the isomerization mechanism allows a rationalization of the very short lifetime of the stilbene triplets, estimated from the azulene quenching studies to be $\leq 7.7 \times 10^{-8}$ sec. If, as seems reasonable, p is assumed to have a twisted configuration with an angle of twist $\sim \pi/2$, it may be very close, both in energy and configuration, to a point on the potential surface of the ground singlet state (fig 2); intersystem crossing from the triplet to the ground state is expected to be very rapid under such conditions. Saltiel believes that there may be an actual crossing of the singlet and triplet states in this region as shown in fig 2;[20a] the energy of the twisted ground state has been estimated from thermal isomerization studies to be $\sim$49 kcal/mole above that of *trans*-stilbene.[23]

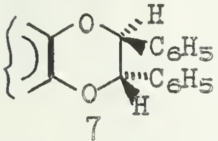
Recent work by Saltiel has provided additional evidence as to the nature of p and the decay processes involved in the stilbene isomerization.[20] The photostationary state composition obtained from isomerization of trans-stilbene-$\underline{d}_{12}$ was found to equal that obtained from undeuterated *trans*-stilbene for sensitizers of $E_T^S = 48$-69 kcal/mole;



Stilbene Energy Profile
fig 2

the quantum yields of the two isomerizations were also identical. Deuteration is known to decrease the rate of triplet to singlet radiationless decay, the effect diminishing as the energy separation between the two states decreases.[24] If p is of lower energy than $\underline{t}^{T1}$, deuteration is predicted to affect decay of $\underline{t}^{T1}$ to *trans*-stilbene more than decay of p to a twisted ground state, assuming decay from both $\underline{t}^{T1}$ and p to be operative. The absence of such a deuterium effect led Saltiel to conclude that decay from $\underline{t}^{T1}$ is negligible for both *trans*-stilbene and *trans*-stilbene-d_{12}. He believes p to be of lower energy than t^{T1} as shown in fig 2 with virtually all decay to the ground state occurring from p, a point of view not fully shared by Hammond.[18] Although decay to the ground state from $\underline{t}^{T1}$(eq 12) has not been rigorously ruled out, decay of the very short-lived *cisoid* triplet to ground state stilbene is not believed to occur, internal conversion to p and/or $\underline{t}^{T1}$ being faster. If formation of *cis*-stilbene is assumed to occur mainly from p, then the earlier finding that the photostationary state becomes richer in *cis*-stilbene at higher temperatures can be attributed to the existence of an activation energy in the interconversion between p and $\underline{t}^{T1}$ as shown in fig 2.

Photosensitized isomerization of the stilbenes by the low-energy sensitizer phenanthraquinone (PAQ, E_T^S = 48.8 kcal/mole) has recently been studied in benzene solution by Bohning and Weiss.[25] Formation of adduct 7 occurred competitively with isomerization.



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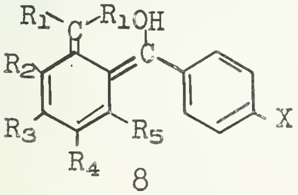
The kinetic results obtained are in substantial agreement with the mechanism already discussed for the isomerization, the only major difference being the inclusion of a short-lived complex, X, formed *via* triplet energy transfer to either *cis*- or *trans*-stilbene, decay of X being partitioned between collapse to 7 and decay to p and PAQ. The existence of X as a common intermediate is strongly suggested by the observation that both *cis*- and *trans*-stilbene give the same adduct. The geometrical changes leading to p are postulated to occur in X, in which there is believed to be freedom of torsional motion in the stilbene accounting for the formation of 7 from both the *cis* and *trans* isomers. Classical energy transfer to *trans*-stilbene(but not to *cis*-stilbene) was also invoked, for in its absence the quantum yields of adduct formation become independent of $(\underline{cis})_s/(\underline{trans})_s$, whereas such a dependence was observed.

The *cis*-*trans* isomerization of stilbene has been used to examine the steric requirements of triplet energy transfer.[26] Theory predicts that this process should be subject to steric hindrance by bulky substituents on the donor or acceptor.[2] In agreement with this idea, it was found that whereas the high-energy sensitizers 2,3,5,6-tetramethyl-4'-methoxybenzophenone (E_T^S = 70.2 kcal/mole) and 2,4,6-trimethyl-4'-methoxybenzophenone (E_T^S = 68.4 kcal/mole) produced the same photostationary state as benzophenone (E_T^S = 68.5 kcal/mole), indicating diffusion-controlled energy transfer, 2,4,6-triisopropyl-4'-methoxybenzophenone (E_T^S = 69.9 kcal/mole) and 2,4,6-triisopropylbenzophenone (E_T^S = 68.7 kcal/mole), compounds which are more hindered about the carbonyl group where the triplet energy is believed to be localized,[2] gave *cis* rich photostationary states indicating that energy transfer to *cis*-stilbene is less efficient than to *trans*-stilbene. To insure that the observed results were not due to selective energy transfer from the low-energy triplets of the photoenols of structure 8 formed from the



8

sensitizer triplets, the rates of quenching of the photoenolization of the triplets of 2,4,6-trimethyl-4'-methoxybenzophenone and 2,4,6-triisopropyl-4'-methoxybenzophenone by added *cis*- and *trans*-stilbene were studied; the rate of decrease of photoenolization (and hence rate of triplet energy transfer) of 2,4,6-trimethyl-4'-methoxybenzophenone was about 15 times as great as that of 2,4,6-triisopropyl-4'-methoxybenzophenone, *trans*-stilbene being the better quencher in each case, confirming the existence of a steric effect to energy transfer.

The photosensitized *cis*-*trans* isomerization of the piperylenes is mechanistically

similar to that of the stilbenes and has been reviewed by Turro,[27] and recently studied on a silica gel-benzene matrix[28] and under ferrocene photosensitized conditions.[29] In addition, the piperylene isomerization has found many uses in photochemistry including measurement of the intersystem crossing quantum yields of sensitizers whose triplet states can effect the isomerization,[5a] and measurement of the triplet energies of sensitizers for which spectral data is not available.[16,27] Owing to their relatively low triplet energies, both *cis*- and *trans*-piperylene (E_T = 56.9 and 58.8 kcal/mole, respectively) have been extensively used as triplet quenchers in mechanistic studies.

The photosensitized conversion of *cis,cis*-1,3-cyclooctadiene to bicyclo[4.2.0]-oct-7-ene has been found by Liu[30] to proceed *via* the isolable *cis,trans*-1,3-cyclooctadiene which is then thermally converted into bicyclo[4.2.0]-oct-7-ene in accord with the Woodward-Hoffmann rules.

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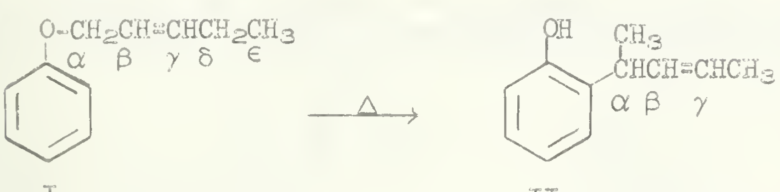
THE ABNORMAL CLAISEN REARRANGEMENT

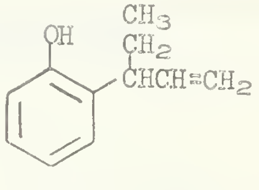
Reported by James E. Shaw May 25, 1967

INTRODUCTION

In 1936 Lauer and Filbert reported that rearrangement of γ-ethylallyl phenyl ether (I) in N,N-diethylaniline at 201-225°C did not result in the normal Claisen rearrangement product, o-(α-ethylallyl)phenol (III), but instead gave o-(α,γ-dimethylallyl)phenol (II).[1-3]

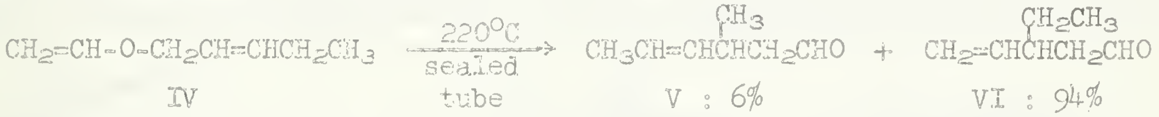


I II



III

The abnormal product II appears to arise from attachment of the β-or δ-carbon of the allyl chain to the ortho carbon of the benzene ring. The normal Claisen rearrangement involves γ-attachment. Lauer and Filbert found that ozonolysis of their product gave small amounts of formaldehyde in addition to the expected acetaldehyde; however, they failed to attribute the formaldehyde as possibly arising from the normal product III. It was later shown by Hurd and Pollack[4] that under the same conditions both the normal and abnormal products are formed in a 1.3 : 1 ratio. These workers also showed that the aliphatic analogue, γ-ethylallyl vinyl ether (IV), rearranged to give some abnormal product V in addition to the major normal Claisen rearrangement product VI.

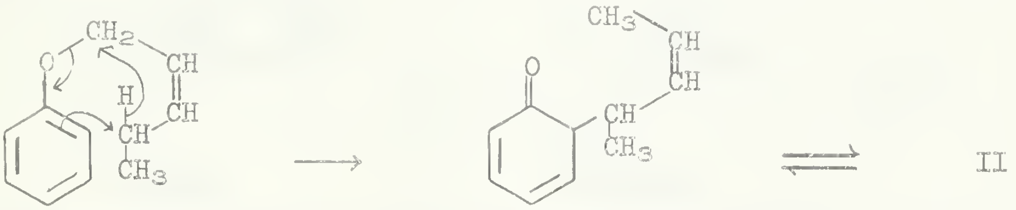


$$\underset{\text{IV}}{CH_2{=}CH{-}O{-}CH_2CH{=}CHCH_2CH_3} \xrightarrow[\text{sealed tube}]{220^\circ C} \underset{\text{V : 6\%}}{CH_3CH{=}CH\overset{CH_3}{C}HCH_2CHO} + \underset{\text{VI : 94\%}}{CH_2{=}CH\overset{CH_2CH_3}{C}HCH_2CHO}$$

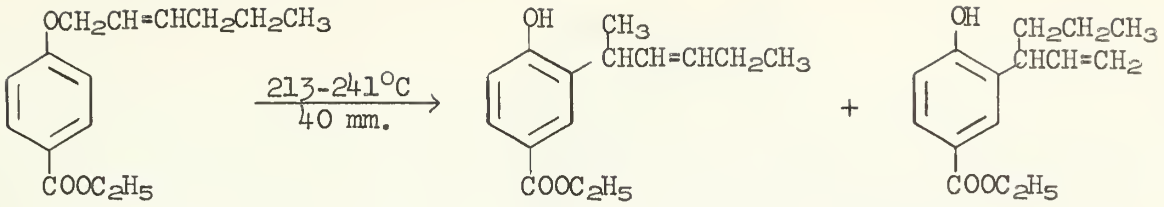
Several other examples of the abnormal Claisen rearrangement are given in the literature.[5-10] In all of these cases the allyl phenyl ether which undergoes rearrangement contains a γ-substituted methyl, ethyl, or n-propyl group. No abnormal Claisen rearrangements have been reported for α- or β-alkyl substituted or γ-aryl substituted allyl phenyl ethers.[11,12] It appears that γ-secondary or γ-tertiary alkyl substituted allyl phenyl ethers have not been investigated. The purpose of this seminar will be to examine the mechanism of the abnormal Claisen rearrangement in both aromatic and aliphatic systems.

MECHANISM

For the rearrangement of γ-ethylallyl phenyl ether Hurd and Pollack proposed the following cyclic mechanism which involves attachment of the δ-carbon of the cis configuration of the allyl chain to the ortho carbon of the benzene ring.[4]

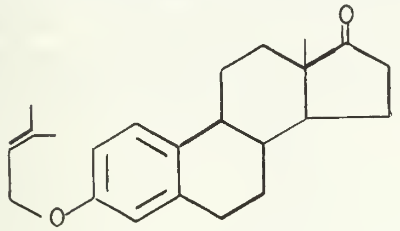


However, the abnormal rearrangements of ethyl p-(γ-n-propylallyloxy)benzoate (VII) and γ,γ-dimethylallyl estrone ether (VIII) have shown that this mechanism is incorrect, and that the abnormal product results from β-attachment of the allyl group.[5,10] For compound VII the abnormal product IX could result from attachment of the β- or ε-carbon. If the abnormal rearrangements of both the γ-propyl and γ-ethylallyl phenyl ethers are proceeding by a single mechanism β-attachment must

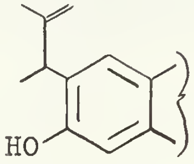

$OCH_2CH=CHCH_2CH_2CH_3$
$COOC_2H_5$
213-241°C
40 mm.
OH
CH_3
$CHCH=CHCH_2CH_3$
$COOC_2H_5$
+
OH
$CH_2CH_2CH_3$
$CHCH=CH_2$
$COOC_2H_5$

VII IX X

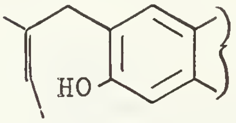
be involved. The abnormal rearrangement of ether VIII would result in product XI if β-attachment occurred, and product XII is there was δ-attachment.



VIII



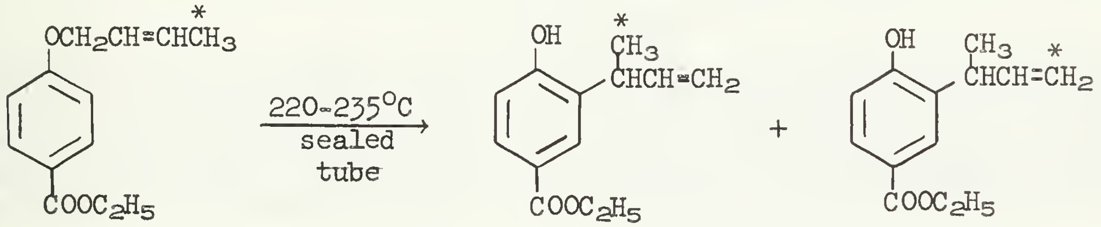
XI



XII

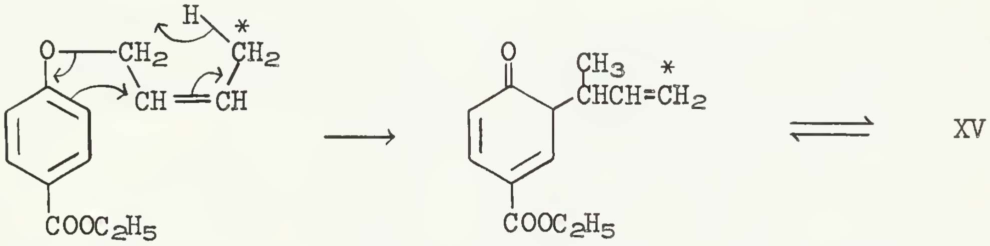
Since the observed product was XI, it appears that the abnormal rearrangement involves attachment of the β-carbon of the allyl chain to the benzene ring.

Lauer and co-workers investigated the possibility that the rearrangement of the crotyl phenyl ether XIII, the simplest of the γ-substituted allyl phenyl ethers, was proceeding by the abnormal path involving β-attachment of the allyl group rather than by the normal route involving γ-attachment.[13] In both cases the product would be the same. However, if the γ-substituted methyl group were tagged with ^{14}C, the normal rearrangement would give XIV while the abnormal rearrangement should give XV.

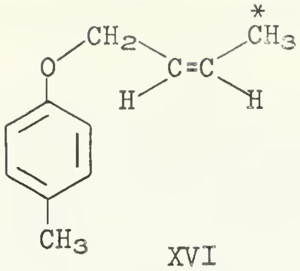

*
$OCH_2CH=CHCH_3$
$COOC_2H_5$
220-235°C
sealed
tube
OH
*
CH_3
$CHCH=CH_2$
$COOC_2H_5$
+
OH
CH_3 *
$CHCH=CH_2$
$COOC_2H_5$

XIII XIV XV

Ozonolysis of the product, followed by a study of the radioactivity of the formaldehyde produced, showed that 15-29% of the product had been produced by the abnormal rearrangement process. To account for the abnormal rearrangement, Lauer proposed the following mechanism which involves β-attachment of the cis configuration of the allyl chain.

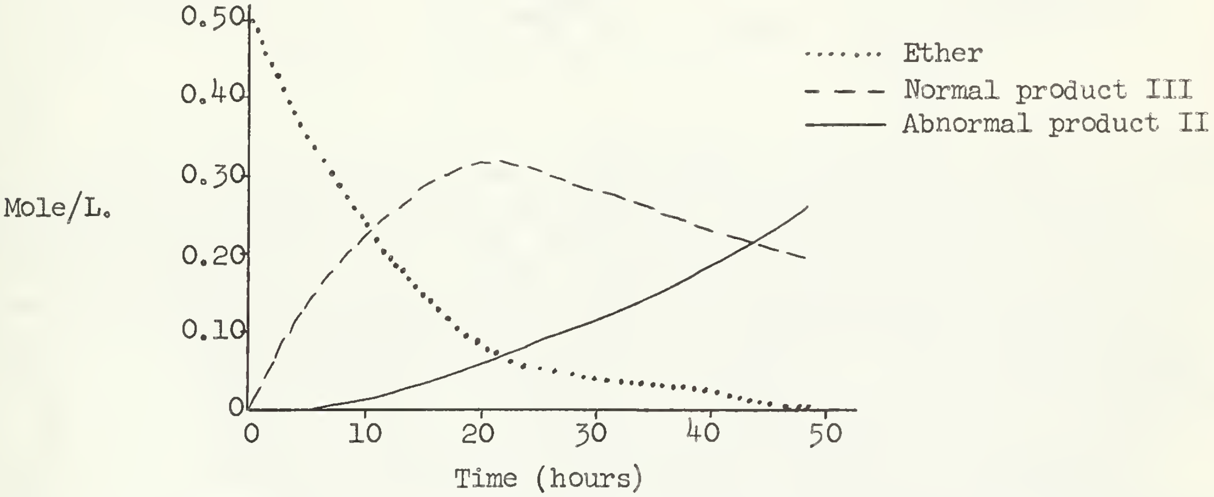

O
CH_2
H
*
CH_2
CH
CH
$COOC_2H_5$
O
CH_3 *
$CHCH=CH_2$
$COOC_2H_5$
XV

However, in Lauer's work it was not shown whether ether XIII was cis or trans. Schmid and co-workers[14,15] studied the rearrangement of the cis isomer of γ-^{14}C-methylallyl p-tolyl ether (XVI). Heating the ether for three hours at 230°C in N,N-diethylaniline gave a rearrangement product, 2-(α-methylallyl)-4-methylphenol, which showed by examination of the formaldehyde produced upon ozonolysis, that 40% of the reaction was apparently proceeding by the abnormal route in comparison to Lauer's 15-29%.

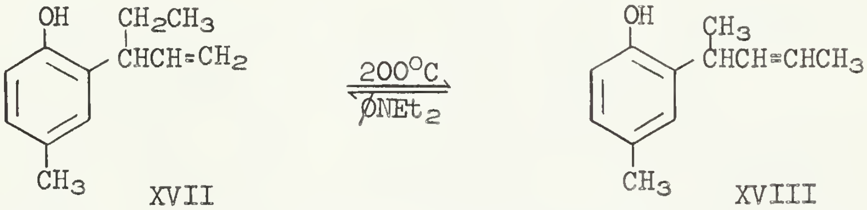


XVI

Marvell and co-workers[16] were the first to show that the abnormal Claisen product was not formed directly from the allyl phenyl ether, but instead was due to further rearrangement of the initially formed normal Claisen product. The rearrangement of γ-ethylallyl phenyl ether (I) in N,N-diethylaniline at 195°C was followed by infrared measurements and gave the data shown in the graph below.

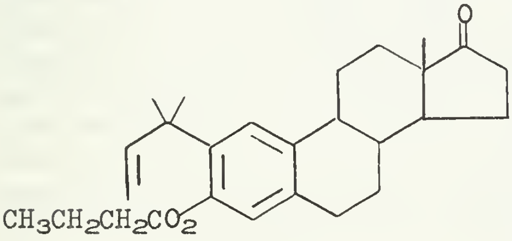


Furthermore, if the normal Claisen product III was heated in N,N-diethylaniline or neat at 200-225°C, it slowly rearranged to the abnormal product II. Roberts and Landolt[17] have found that heating either XVII or XVIII, the normal and abnormal products of γ-ethylallyl p-tolyl ether, results in the same equilibrium mixture of the two with the abnormal product being favored by a ratio of 24 : 1.



XVII XVIII

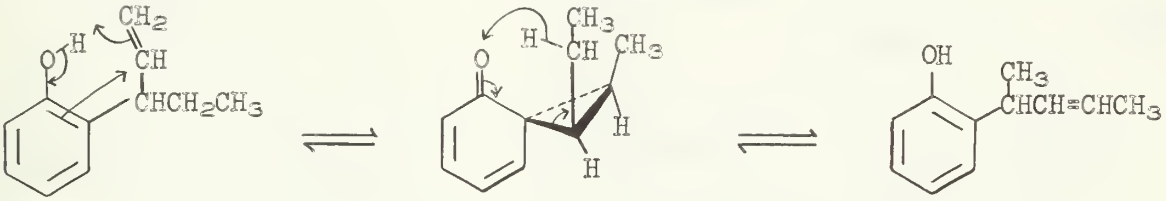
Jefferson and Scheinmann[10] have reported that rearrangement of γ,γ-dimethylallyl estrone ether (VIII) in N,N-diethylaniline produces only the abnormal product XI. However, if the rearrangement is carried out in diethylaniline containing butyric anhydride, the normal Claisen product can be trapped as its butyric ester XIX. The normal Claisen product rapidly isomerized to the abnormal product XI when it was heated in diethylaniline. On the basis of this evidence, Marvell, Roberts, and Jefferson conclude that the abnormal Claisen rearrangement is really the result of two consecutive processes: normal Claisen rearrangement of the γ-alkylallyl aryl ether to the o-(α-alkylallyl)phenol, followed by rearrangement of this phenol to produce the isomeric phenol. Although the evidence strongly supports this conclusion, it cannot rule out another possibility in which the normal product reversibly forms the allyl aryl ether which then reacts



XIX

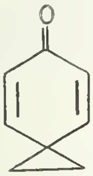
by some mechanism to give the abnormal product directly. However, in equilibration experiments such as that involving XVII and XVIII, no ether has ever been reported found.[14,17]

Marvell and co-workers[16] also reported that the methyl ether of o-(α-ethylallyl)phenol (III) was recovered unaltered upon heating it under the conditions which converted o-(α-ethylallyl)phenol to the abnormal product II. This indicated that the rearrangement of the normal product to the abnormal product depends on the phenolic hydroxyl group. Also, 2,6-dimethyl-4-(α-ethylallyl)phenol was stable under the same conditions showing that the allyl side chain must be ortho to the hydroxyl group in order for rearrangement to occur. Marvell proposed the following mechanism for the rearrangement between the normal and abnormal products.



III XX II

Infrared studies of o-allylphenols have revealed that the phenolic proton is hydrogen bonded to the allyl π-bond, thus indicating that the molecule is in the proper conformation for reaction.[18] When the spirodienone intermediate XX is formed from III, the ethyl group could also be trans to the methyl group, but this configuration would not allow further rearrangement to II by the intramolecular process shown.

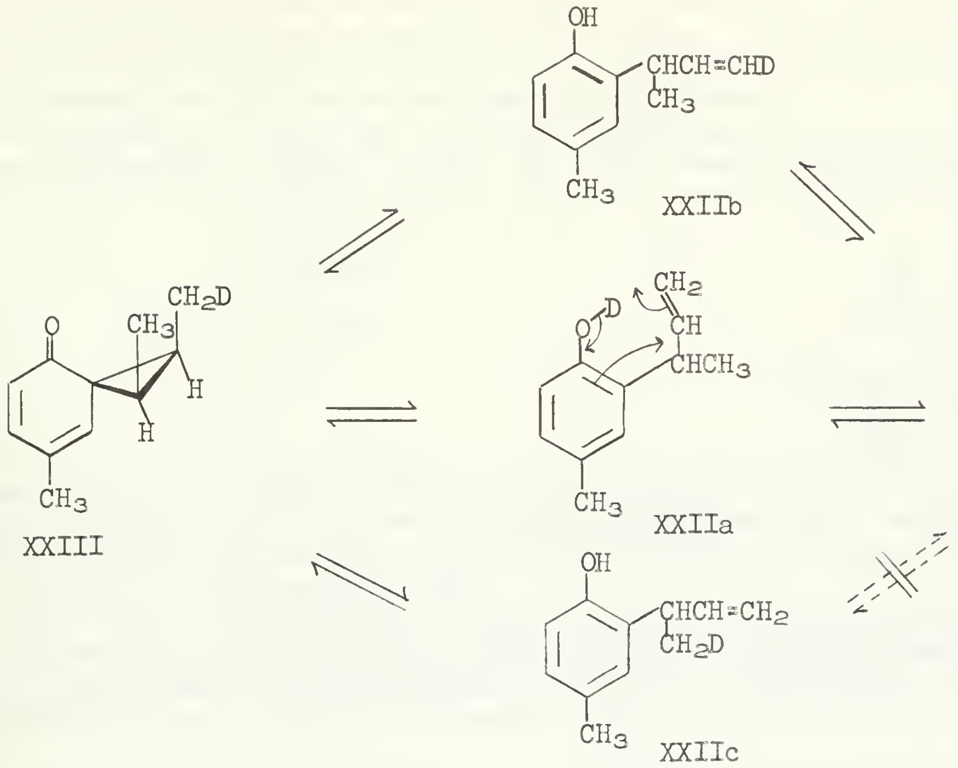


XXI

The intermediate XX is similar to spiro[2.5]octa-1,4-dien-3-one (XXI) isolated by Winstein and Baird.[19,20] Since this compound decomposed upon standing at room temperature, it is quite unlikely that a spirodienone intermediate such as XX could be isolated under the conditions of the abnormal Claisen rearrangement.

Marvell's mechanism is strongly supported by experiments dealing with ^{14}C labeling, deuterium incorporation, and cis-trans isomerization of substituted o-allylphenols. Lauer and Johnson[21] have shown that heating γ-^{14}C-methylallyl p-carbethoxyphenyl ether (XIII) for 280 hours at 220°C results in a 50:50 distribution of ^{14}C between the two positions shown in XIV and XV. This is the result predicted by Marvell's mechanism since as shown in intermediate XX (replace ethyl by methyl), the ^{14}C labeled methyl group can become one of two symmetrically equivalent methyl groups. This should allow equal distribution of the radioactive label between the methyl and methylene positions in XIV and XV. Similar results have been obtained by Schmid.[14]

Schmid and co-workers[22,23] have studied the incorporation of deuterium into 2-(α-methylallyl)-4-methylphenol (XXII). As shown below the deuterated phenol XXIIa can form either the cis spirodienone intermediate XXIII or the trans intermediate XXIV by intramolecular transfer of the deuterium atom. The trans intermediate would probably be formed more often because it is very likely that the cis intermediate is of higher energy, due to steric factors. In the cis intermediate, proton transfers from the methyl groups can produce phenols XXIIb or XXIIc. However, in the trans intermediate only phenol XXIIb can be formed by an intramolecular proton transfer. Therefore, if 2-(α-methylallyl)-4-methylphenol (XXII) is heated in D_2O, deuterium should be initially incorporated more rapidly at the methylene position ($=CH_2$) than at the α-methyl. However, at equilibrium the amount of deuterium incorporated at the methylene carbon should be statistically equal to that at the methyl. In other words, if n equals the amount of deuterium on the methylene carbon and m the amount on the methyl, then at equilibrium 3n should equal 2m or 3n/2m should equal one assuming no deuterium isotope effects.


OH
CHCH=CHD
CH3
CH3
XXIIb
CH2D
O
CH3
H
H
CH3
XXIII
CH2
D
CH
CHCH3
O
CH3
XXIIa
O
CH2D
H
H
CH3
CH3
XXIV
OH
CHCH=CH2
CH2D
CH3
XXIIc

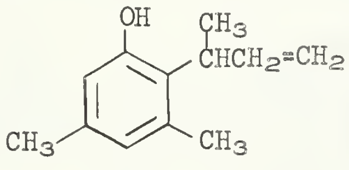
By heating 2-(α-methylallyl)-4-methylphenol (XXII) in D_2O at 200°C for various periods of time and determining the deuterium content and distribution by combustion and nmr, Schmid obtained the results shown in Table I.

Table I

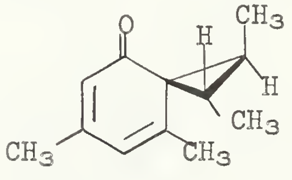
Time heated (hours)	% D in side chain 100% = 5 D	3n/2m
4	4.6	≥ 5
24	49.4	1.78
48	68.6	1.18

No deuterium was incorporated at the α or β positions of the allyl group. The fact that 3n/2m equals approximately five after four hours heating indicates that deuterium is initially incorporated more rapidly at the methylene position as predicted. When the deuterated phenol which possessed a 3n/2m value of 1.18 was heated in water for ten hours, the 3n/2m value changed to 0.67, showing that deuterium is more rapidly removed from the methylene carbon than the methyl carbon as would be predicted.

Schmid also studied deuterium incorporation into 3,5-dimethyl-2-(α-methylallyl)-phenol (XXV).[22,23]


OH
CH3
CHCH2=CH2
CH3
CH3

XXV

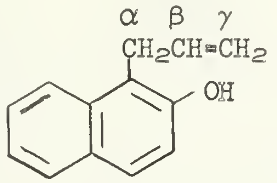

O
H
CH3
H
CH3
CH3
CH3

XXVI

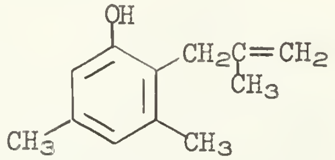
In this case the trans intermediate XXVI should be disfavored due to repulsion between the cyclopropyl methyl group and the methyl group at the 3-position of the benzene ring. It would be expected therefore that an increased amount of cis intermediate possessing symmetrically equivalent methyl groups should help to equalize the rates at which deuterium is incorporated at the methylene and methyl positions. In other words, the value of 3n/2m should approach a value of one much

more quickly for XXV than it did for XXII. It was found that when XXV was heated in D_2O at 200°C for only twelve hours, $3n/2m$ equaled 1.04. If this result is compared with those for phenol XXII in Table I, it is apparent that the formation of the *trans* intermediate XXVI was significantly suppressed.

By the Marvell mechanism, any *o*-allylphenol should be able to form a spirodienone intermediate similar to XX. For this reason compounds XXVII and XXVIII could be expected to incorporate deuterium at the γ-carbon of the allyl group.[22,23]



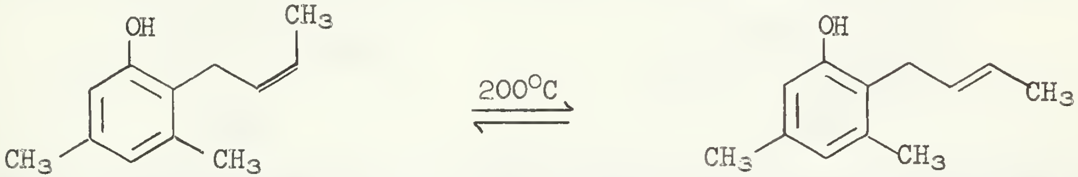
XXVII



XXVIII

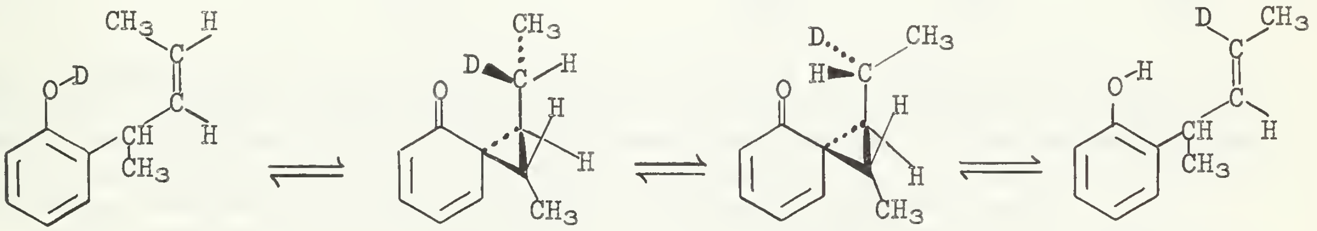
Heating 1-allyl-2-naphthol (XXVII) in D_2O at 200°C for 48 hours, resulted in almost complete incorporation of deuterium at this position only. When XXVIII was heated in D_2O at 200°C for 48 hours, 1.85 deuterium atoms were found on the γ-carbon and less than 0.1 on the β-methyl group.

The thermal interconversion of *cis* and *trans* *o*-(γ-alkylallyl)phenols can also be explained by the Marvell mechanism. Schmid and Frater[24] found that heating either *cis*- or *trans*-XXIX in diethylaniline at 200°C for several days resulted in the same equilibrium mixture of the two isomers.



cis-XXIX $K_{trans/cis}=3.6$ trans-XXIX

The methyl ethers of *cis*- or *trans*-XXIX did not interconvert under these conditions, showing that the hydroxyl group is necessary for the isomerization. Marvell's mechanism can account for this *cis-trans* interconversion, since the γ-carbon of the allyl group becomes a saturated center in the spirodienone intermediate. Marvell[25,26] has shown that heating either *cis* or *trans* *o*-(α-γ-dimethylallyl)phenol (II) at 210°C produces the same equilibrium mixture of 22% *cis*-II and 78% *trans*-II. The isomerization of *cis*-II in water and D_2O at 205°C followed first order kinetics with k_H/k_D equal to 2.8. The rate of formation of *trans*-II from *cis*-II in D_2O was found to be equal to the rate of olefinic deuterium incorporation as measured by nmr. The nmr of *trans*-II which was isolated after 0.7, 2.0, 3.6, and 4.8 half lives showed the presence of one olefinic proton. The γ-methyl appeared as a clean singlet. This showed that there was one deuterium at the γ-carbon of each molecule of *trans*-II. These data show that every molecule of *cis*-II which is converted to *trans*-II incorporates one deuterium into the allyl side chain at the γ-carbon as shown below.

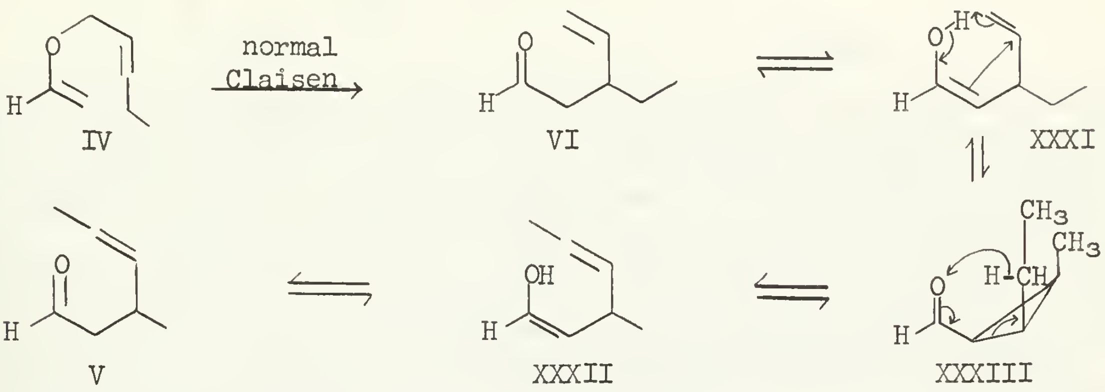


XXX

Therefore, the proton transfer in intermediate XXX to give the *trans* isomer must be completely stereoselective within the limits of the experiment.

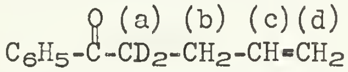
ALIPHATIC ANALOGUES

Marvell's mechanism can account for the formation of the abnormal product V in the rearrangement of γ-ethylallyl vinyl ether (IV) as shown below.



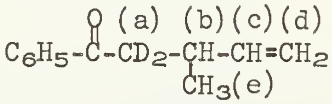
The enols XXXI and XXXII are directly analogous to the o-allylphenols obtained in the rearrangement of γ-ethylallyl phenyl ether (I).

That the above mechanism is indeed involved in aliphatic systems is supported by deuterium isotope experiments by Roberts and co-workers.[27,28] These workers heated 4-pentenophenone-2-d_2(XXXIV) and 3-methyl-4-pentenophenone-2-d_2(XXXV) in sealed tubes at 202°C and followed the changes in the deuterium distribution by nmr.



$$\overset{\overset{(a)}{}}{C_6H_5\text{-}\overset{O}{\overset{\|}{C}}\text{-}\overset{(b)}{CD_2}\text{-}\overset{(c)}{CH_2}\text{-}\overset{(d)}{CH{=}CH_2}}$$

XXXIV



$$C_6H_5\text{-}\overset{O}{\overset{\|}{C}}\text{-}\overset{(a)}{CD_2}\text{-}\underset{CH_3(e)}{\overset{(b)}{CH}}\text{-}\overset{(c)}{CH}{=}\overset{(d)}{CH_2}$$

XXXV

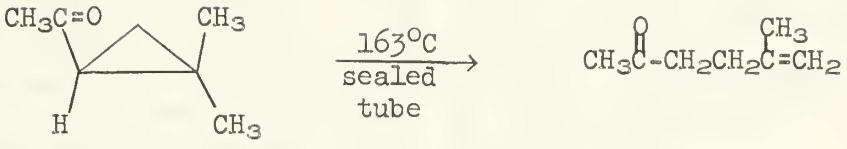
By applying the Marvell mechanism, it can be predicted that at equilibrium compound XXXIV should have one deuterium at each of positions (a) and (d) and no deuterium at positions (b) and (c). Compound XXXV at equilibrium should have 0.57 deuteriums at each of positions (a) and (d), 0.86 deuteriums at position (e), and no deuterium at positions (b) and (c). The experimental results are given in Table II.

Table II

Compound	Time heated (hours)	Deuterium (g-atom)		
		CH_2 (a)	CH_2 (d)	CH_3 (e)
XXXIV	17	1.73	0.20	--
"	72	1.23	0.74	--
"	145	0.97	0.90	--
XXXV	12	1.27	0.60	0.12
"	48	0.83	0.63	0.52
"	121	0.58	0.63	0.66

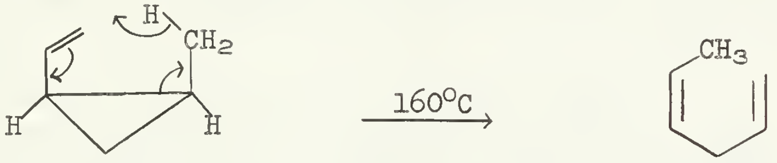
Both compounds had no deuterium in positions (b) and (c). These results are in fairly good agreement with those predicted by the Marvell mechanism. However, the results are complicated by the fact that mass spectroscopy of the product obtained after heating XXXIV for 72 hours showed the presence of d_0, d_3, and d_4 molecules indicating that intermolecular deuterium exchange had also occurred.

Other experimental work by Roberts and co-workers supports the intermediacy of the cyclopropyl compound XXXIII in the Marvell mechanism.[28,29] 1-Acetyl-2,2-dimethylcyclopropane (XXXVI) smoothly rearranged to 5-methyl-5-hexen-2-one (XXXVII) at temperatures above 150°C. The reaction follows first order kinetics and has an activation energy of 30 kcal/mole and an entropy of activation of -10 eu. The structure of compound XXXVI is such that one methyl group must be cis to the carbonyl



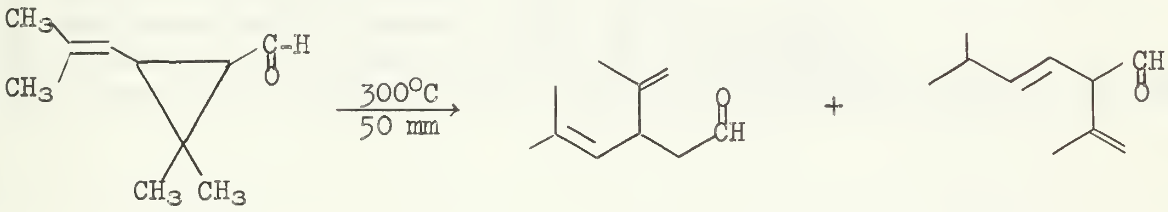
XXXVI XXXVII

group and thus in a favorable position for the intramolecular 1,5-hydrogen shift as shown in intermediate XXXIII. That a cis relationship is required between the carbonyl and methyl groups in order for the rearrangement to occur is shown by the thermal isomerization of the cis and trans isomers of 1-acetyl-2-methylcyclopropane.[28,29] At 160°C, the cis isomer rearranged almost completely in twelve hours to the expected 5-hexen-2-one, but at 180°C, the trans isomer decomposed only slightly over a period of 24 hours and the product was not 5-hexen-2-one. Other examples of this same type of rearrangement are reported in the literature.[30-32] The rearrangement of 1-acetyl-2,2-dimethylcyclopropane (XXXVI) is analogous to the rearrangement of cis-1-methyl-2-vinylcyclopropane (XXXVIII) involving the homodienyl-1,5-hydrogen shift.[33,34]



XXXVIII

This rearrangement follows first order kinetics and has an energy of activation of 30 kcal/mole and an entropy of activation of -12 eu., which are very similar to those values previously mentioned for XXXVI. trans-1-Methyl-2-vinylcyclopropane is stable at 250°C. Ohloff[31] has studied the thermal rearrangement of cyclopropane XXXIX which contains both vinyl and carbonyl groups cis to methyl groups.



XXXIX XL XLI

The major product XL was due to reaction involving the carbonyl group. The other product XLI, which was due to reaction of the vinyl group, was formed in approximately 10% yield.

SUMMARY

The abnormal Claisen rearrangement has been identified as the result of two consecutive processes: normal Claisen rearrangement of the γ-alkylallyl aryl ether to an o-(α-alkylallyl)phenol, followed by rearrangement of the side chain of this phenol to produce an isomeric phenol. The mechanism of the secondary rearrangement has been formulated as involving a substituted spiro[2.5]octa-4,6-dien-3-one intermediate. Considerable experimental work has provided strong support for this mechanism. Abnormal Claisen rearrangements involving aliphatic systems appear to be closely analogous to the aromatic case.

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